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(54) Title: SUBSTITUTED AMIDES ACTIVE AT THE CANNABINOID-1 RECEPTOR

(57) Abstract: Novel compounds of the structural formula (I) are antagonists and/or inverse agonists of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the CB1 receptor. The compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson s disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, the treatment of obesity or eating disorders, as well as the treatment of asthma, constipation, chronic intestinal pseudo-obstruction, and cirrhosis of the liver.

SUBSTITUTED AMIDES ACTIVE AT THE CANNABINOID-1 RECEPTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

Not applicable.

BACKGROUND OF THE INVENTION

Marijuana (*Cannabis sativa L.*) and its derivatives have been used for centuries for medicinal and recreational purposes. A major active ingredient in marijuana and hashish has been determined to be Δ^9-tetrahydrocannabinol (Δ^9-THC). Detailed research has revealed that the biological action of Δ^9-THC and other members of the cannabinoid family occurs through two G-protein coupled receptors termed CB1 and CB2. The CB1 receptor is primarily found in the central and peripheral nervous systems and to a lesser extent in several peripheral organs. The CB2 receptor is found primarily in lymphoid tissues and cells. Three endogenous ligands for the cannabinoid receptors derived from arachidonic acid have been identified (anandamide, 2-arachidonoyl glycerol, and 2-arachidonyl glycerol ether). Each is an agonist with activities similar to Δ^9-THC, including sedation, hypothermia, intestinal immobility, antinociception, analgesia, catalepsy, anti-emesis, and appetite stimulation.

The genes for the respective cannabinoid receptors have each been disrupted in mice. The $CB1^{-/-}$ receptor knockout mice appeared normal and fertile. They were resistant to the effects of Δ^9-THC and demonstrated a strong reduction in the reinforcing properties of morphine and the severity of withdrawal syndrome. They also demonstrated reduced motor activity and hypoalgesia. Excessive exposure to Δ^9-THC can lead to overeating, psychosis, hypothermia, memory loss, and sedation. There is at least one CB1 modulator characterized as an inverse agonist or an antagonist, N-(1-piperidinyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (SR141716A), in clinical trials for treatment of eating disorders at this time. There still remains a need for potent low molecular weight CB1 modulators that have pharmacokinetic and pharmacodynamic properties suitable for use as human pharmaceuticals.

Treatment of asthma with CB1 receptor modulators (such as CB1 inverse agonists) is supported by the finding that presynaptic cannabinoid CB1

receptors mediate the inhibition of noradrenaline release (in the guinea pig lung) (Europ. J. of Pharmacology, 2001, 431 (2), 237-244).

Treatment of cirrhosis of the liver with CB1 receptor modulators is supported by the finding that a CB1 receptor modulator will reverse the low blood pressure observed in rats with carbon tetrachloride-induced liver cirrhosis and will lower the elevated mesenteric blood flow and portal vein pressure (Nature Medicine, 2001, 7 (7), 827-832).

US Patents US 5,624,941 and US 6,028,084, PCT Application Nos. WO98/43636 and WO98/43635, and EPO Application No. EP-658546 disclose substituted pyrazoles having activity against the cannabinoid receptors.

PCT Application Nos. WO98/31227 and WO98/41519 also disclose substituted pyrazoles having activity against the cannabinoid receptors.

PCT Application Nos. WO98/37061, WO00/10967, and WO00/10968 disclose diaryl ether sulfonamides having activity against the cannabinoid receptors.

PCT Application Nos. WO97/29079 and WO99/02499 disclose alkoxy-isoindolones and alkoxy-quinolones as having activity against the cannabinoid receptors.

US Patent US 5,532,237 discloses N-benzoyl-indole derivatives having activity against the cannabinoid receptors.

US Patents US 4,973,587, US 5,013,837, US 5,081,122, and US 5,112,820, US 5,292,736 disclose aminoalkylindole derivatives as having activity against the cannabinoid receptors.

PCT publication WO 01/58869 discloses pyrazoles, pyrroles and imidazole cannabinoid receptor modulatorsuseful for treating respiratory and non-respiratory leukocyte activation-associated disorders.

PCT publications WO 01/64632, 01/64633, and 01/64634 assigned to Aventis are directed to azetidine derivatives as cannabinoid antagonists.

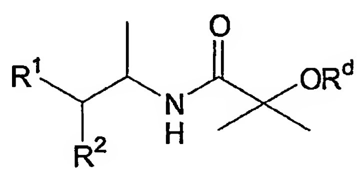
Schultz, E.M, *et al.* *J. Med Chem.* 1967, *10*, 717 and Pines, S. H. *et al.* *J. Med. Chem.* 1967, *10*, 725 disclose maleamic acids affecting plasma chloesterol and penicillin excretion.

The compounds of the present invention are modulators of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the Cannabinoid-1 (CB1) receptor. In particular, compounds of the present invention are antagonists or inverse agonists of the CB1

receptor. The invention is concerned with the use of these compounds to modulate the Cannabinoid-1 (CB1) receptor. As such, compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, particularly to opiates, alcohol, marijuana, and nicotine. The compounds are also useful for the treatment of eating disorders by inhibiting excessive food intake and the resulting obesity and complications associated therewith. The compounds are also useful for the treatment of constipation and chronic intestinal pseudo-obstruction, as well as for the treatment of asthma, and cirrhosis of the liver.

SUMMARY OF THE INVENTION

The present invention is concerned with novel substituted amides of the general Formula I :



(I)

and pharmaceutically acceptable salts thereof which are antagonists and/or inverse agonists of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the Cannabinoid-1 (CB1) receptor. The invention is concerned with the use of these novel compounds to selectively antagonize the Cannabinoid-1 (CB1) receptor. As such, compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders,

and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, particularly to opiates, alcohol, marijuana, and nicotine, including smoking cessation. The compounds are also useful for the treatment of obesity or eating disorders associated with excessive food intake and complications associated therewith. The compounds are also useful for the treatment of constipation and chronic intestinal pseudo-obstruction. The compounds are also useful for the treatment of cirrhosis of the liver. The compounds are also useful for the treatment of asthma.

The present invention is also concerned with treatment of these conditions, and the use of compounds of the present invention for manufacture of a medicament useful in treating these conditions. The present invention is also concerned with treatment of these conditions through a combination of compounds of formula I and other currently available pharmaceuticals.

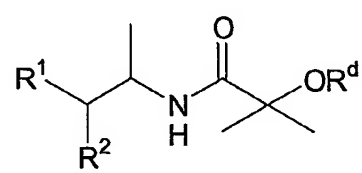
The invention is also concerned with novel compounds of structural formula I.

The invention is also concerned with pharmaceutical formulations comprising one of the compounds as an active ingredient.

The invention is further concerned with processes for preparing the compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

The compounds used in the methods of the present invention are represented by the compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein;

R^1 is selected from:

(1) cycloheteroalkyl,

(2) aryl,

(3) heteroaryl, and

(4) $-NR^aR^c$;

wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from R^b;

R^2 is selected from:

(1) C_{1-10}alkyl,

(2) C_{3-10}cycloalkyl-C_{1-4}alkyl,

(3) aryl-C_{1-4}alkyl, and

(4) heteroaryl-C_{1-4}alkyl;

wherein each cycloalkyl, aryl and heteroaryl is optionally substituted with one to three substituents independently selected from R^b;

each R^a is independently selected from:

(1) hydrogen,

(2) methyl, and

(3) $-CF_3$;

each R^b is independently selected from:

(1) halogen,

(2) cyano,

(3) trifluoromethyl,

(4) trifluoromethoxy,

(5) C_{1-3}alkyloxy, and

(6) C_{1-3}alkyl;

R^c is independently selected from:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) aryl,

(4) heteroaryl,

(5) aryl-methyl, and

(6) heteroaryl-methyl,

each R^c may be unsubstituted or substituted with one to three substituents selected from R^h;

R^d is independently selected from:

(1) cycloalkyl,

(2) aryl, and

(3) heteroaryl,

each R^d may be unsubstituted or substituted with one to three substituents selected from R^h;

each R^h is independently selected from:

(1) halogen,

(2) C_{1-3}alkyl,

(3) -CN, and

(4) $-CF_3$,

wherein when pyridyl groups are unsubstituted on the nitrogen, they are optionally present as the N-oxide.

In one embodiment of the present invention, R^1 is selected from:

(1) phenyl,

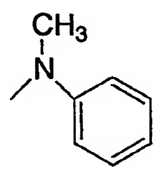
(2) pyridyl,

(3) indolyl,

(4) 7-aza-indolyl,

(5) thiophenyl, and

(6)


;

wherein each aryl and heteroaryl is optionally substituted with one or two substitutents independently selected from R^b, and each pyridyl is optionally present as the N-oxide.

In one class of this embodiment of the present invention, R^1 is selected from:

(1) phenyl,

(2) 3-cyanophenyl,

(3) 3-methylphenyl,

(4) 3,5-difluorophenyl,

(5) 3-pyridyl,

(6) 5-chloro-3-pyridyl,

(7) 5-methyl-3-pyridyl,

(8) 5-cyano-3-pyridyl,

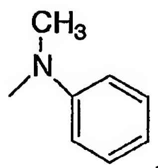
(9) 1-oxido-5-cyano-3-pyridyl,

(10) 1-indolyl,

(11) 7-aza-indol-N-yl,

(12) 2-thiophenyl, and

(13)



In a subclass of this class of the present invention, R^1 is 5-cyano-3-pyridyl.

In another embodiment of the present invention, R^2 is selected from:

(1) C_{1-6}alkyl,

(2) C_{3-6}cycloalkylmethyl,

(3) phenylmethyl,

(4) heteroarylmethyl,

wherein each cycloalkyl, phenyl and heteroaryl is optionally substituted with one to three substituents independently selected from R^b.

In one class of this embodiment of the present invention, R^2 is selected from:

(1) C_{1-6}alkyl,

(2) C_{4-6}cycloalkylmethyl,

(3) phenylmethyl,

(4) pyridyl,

wherein each cycloalkyl, phenyl and heteroaryl is optionally substituted with one or two substituents independently selected from R^b.

In a subclass of this class of the present invention, R^2 is selected from:

(1) 2-methylpropyl,

(2) n-pentyl,

(3) cyclobutylmethyl,

(4) cyclopentylmethyl,

(5) cyclohexylmethyl,

(6) benzyl,

(7) 4-chlorobenzyl,

(8) 4-methylbenzyl,

(9) 4-fluorobenzyl,
(10) 4-methoxybenzyl, and
(11) (5-chloro-2-pyridyl)methyl.

In one embodiment of the present invention, each R^a is independently selected from:

(1) hydrogen,
(2) methyl, and
(3) $-CF_3$.

In one class of this embodiment of the present invention, each R^a is independently selected from:

(1) hydrogen, and
(2) methyl.

In one embodiment of the present invention, each R^b is independently selected from:

(1) halogen,
(2) cyano,
(3) C_{1-3}alkyloxy and
(4) C_{1-3}alkyl.

In one class of this embodiment of the present invention, each R^b is independently selected from:

(1) fluoro,
(2) chloro,
(3) bromo,
(4) iodo,
(5) cyano,
(6) methoxy, and
(7) methyl.

In one subclass of this class, each R^b is independently selected from:

(1) fluoro,
(2) chloro,
(3) cyano,
(4) methoxy, and
(5) methyl.

In one embodiment of the present invention, each R^c is independently selected from:

(1) hydrogen,
(2) C_{1-6}alkyl,
(3) phenyl,
(4) pyridyl,
(5) benzyl, and
(6) pyridyl-methyl;

each R^c may be unsubstituted or substituted with a substituent selected from R^h.

In one class, R^c is phenyl.

In one embodiment of the present invention, R^d is selected from:

(1) C_{4-6}cycloalkyl,,
(2) aryl, and
(3) heteroaryl,

wherein R^d may be unsubstituted or substituted with one or two substituents selected from R^h.

In one class of the present invention, R^d is selected from:

(1) phenyl,
(2) pyridyl, and
(3) pyrimidinyl,

wherein R^d may be unsubstituted or substituted with one or two substituents selected from R^h.

In one subclass of the present invention, R^d is selected from:

(1) phenyl,
(2) 4-chlorophenyl,
(3) 3-chlorophenyl,
(4) 3,5-difluorophenyl,
(5) 3,5-dichlorophenyl,
(6) 2-pyridyl,
(7) 5-chloro-2-pyridyl,
(8) 6-methyl-2-pyridyl,
(9) 5-trifluoromethyl-2-pyridyl,
(10) 4-trifluoromethyl-2-pyridyl,
(11) 4-trifluoromethyl-2-pyrimidyl, and
(12) 6-trifluoromethyl-4-pyrimidyl.

In another subclass of the present invention, R^d is 5-trifluoromethyl-2-pyridyl.

In one embodiment of the present invention, each R^h is independently selected from:

(1) halogen,
(2) C_{1-3}alkyl,
(3) -CN, and
(4) $-CF_3$.

In one class of this embodiment, each R^h is independently selected from:

(1) fluoro,
(2) chloro,
(3) methyl,
(4) -CN, and
(5) $-CF_3$.

Particular novel compounds which may be employed in the methods, uses and compositions of the present invention, include:

(1) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(4-chlorophenyloxy)-2-methylpropanamide;
(2) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(2-pyridyloxy)-2-methylpropanamide;
(3) *N*-[3-(4-chlorophenyl)-1-methyl-2-(3-pyridyl)propyl]-2-(4-chlorophenyloxy)-2-methylpropanamide;
(4) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3,5-difluorophenyloxy)-2-methylpropanamide;
(5) *N*-[3-(4-chlorophenyl)-2-phenyl-1-methylpropyl]-2-(3,5-dichlorophenyloxy)-2-methylpropanamide;
(6) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3-chlorophenyloxy)-2-methylpropanamide;
(7) *N*-[3-(4-chlorophenyl)-2-(3,5-difluorophenyl)-1-methylpropyl]-2-(2-pyridyloxy)-2-methylpropanamide;
(8) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenyl-propyl]-2-(5-chloro-2-pyridyloxy)-2-methylpropanamide;
(9) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(6-methyl-pyridyloxy)-2-methylpropanamide;

(10) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(phenyloxy)-2-methylpropanamide;

(11) *N*-[(3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(5-trifluoromethylpyridyloxy)-2-methylpropanamide;

(12) *N*-[3-(4-chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(13) *N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(14) *N*-[3-(4-chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(15) *N*-[3-(4-chlorophenyl)-2-(5-methyl-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(16) *N*-[3-(4-chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(17) *N*-[3-(4-chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(18) *N*-[3-(4-chlorophenyl)-2-phenyl-1-methylpropyl]-2-(4-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(19) *N*-[3-(4-chlorophenyl)-2-phenyl-1-methylpropyl]-2-(4-trifluoromethyl-2-pyrimidyloxy)-2-methylpropanamide;

(20) N-[3-(4-chlorophenyl)-1-methyl-2-(thiophen-3-yl)propyl]-2-(5-chloro-2-pyridyloxy)-2-methylpropanamide;

(21) *N*-[3-(5-chloro-2-pyridyl)-2-phenyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(22) *N*-[3-(4-methyl-phenyl)-1-methyl-2-phenylpropyl]-2-(4-trifluoromethyl-phenyloxy)-2-methylpropanamide;

(23) *N*-[3-(4-fluoro-phenyl)-2-(3-cyano-phenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(24) N-[3-(4-chlorophenyl)-2-(1-indolyl)-1-methyl)propyl]-2-(5-trifluoromethyl-2-oxypyridine-2–yl)-2-methylpropanamide;

(25) N-[3-(4-chlorophenyl)-2-(7-azaindol-N-yl)-1-methyl)propyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(26) *N*-[3-(4-chloro-phenyl)-2-(1-indolinyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(27) *N*-[3-(4-chloro-phenyl)-2-(N-methyl-anilino)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(28) *N*-[3-(4-methoxy-phenyl)-2-(3-cyano-phenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(29) *N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(6-trifluoromethyl-4-pyrimidyloxy)-2-methylpropanamide;

(30) N-[2-(3-cyanophenyl)-1,4-dimethylpentyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(31) N-[3-(4-chlorophenyl)-2-(1-oxido-5-cyano-3-pyridyl]-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(32) N-[2-(3-cyanophenyl)-3-cyclobutyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(33) N-[2-(3-cyanophenyl)-1-methyl-heptyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(34) N-[2-(3-cyanophenyl)-3-cyclopentyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(35) N-[2-(3-cyanophenyl)-3-cyclohexyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Cycloalkyl" means mono- or bicyclic or bridged saturated carbocyclic rings, each of which having from 3 to 10 carbon atomsExamples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. Examples of aryl include phenyl, naphthyl, and the like.

"Heteroaryl" means a mono- or bicyclic aromatic ring containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, imidazothiazolyl, and the like. In particular,

"heteroaryl" includes pyridyl, pyrimidyl, and thiophenyl, The heteroaryl ring may be substituted on one or more carbon or nitrogen atoms

"Cycloheteroalkyl" means mono- or bicyclic or bridged saturated rings containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. The term also includes monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of "cycloheteroalkyl" include indolyl, azaindolyl and the like. The cycloheteroalkyl ring may be substituted on the ring carbons and/or the ring nitrogens.

"Halogen" includes fluorine, chlorine, bromine and iodine.

When any variable (e.g., R^1, R^d, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C_{1-5} alkylcarbonylamino C_{1-6} alkyl substituent is equivalent to

$$C_{1\text{-}5}\text{alkyl}-\overset{\overset{\displaystyle O}{\|}}{C}\text{-NH-}C_{1\text{-}6}\text{alkyl-}$$

In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers,

diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Tautomers are defined as compounds that undergo rapid proton shifts from one atom of the compound to another atom of the compound. Some of the compounds described herein may exist as tautomers with different points of attachment of hydrogen. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example MeOH or EtOAc or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active amine as a resolving agent or on a chiral HPLC column.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

It is generally preferable to administer compounds of the present invention as enantiomerically pure formulations. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxillary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases

include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. The term "pharmaceutically acceptable salt" further includes all acceptable salts such as acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutamate, stearate, glycollylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, panoate, valerate, and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Compounds of the present invention are modulators of the CB1 receptor. In particular, the compounds of structural formula I are antagonists or inverse agonists of the CB1 receptor.

An "agonist" is a compound (hormone, neurotransmitter or synthetic compound) which binds to a receptor, inducing a conformational change in the receptor which, in turn, produces a response such as contraction, relaxation, secretion, change in enzyme activity, etc. similar to that elicited by the physiologically relevant agonist ligand(s) for that receptor. An "antagonist" is a compound which attenuates

the effect of an agonist. An "inverse agonist" is a compound which acts on a receptor but produces the opposite effect produced by the agonist of the particular receptor.

Compounds of this invention are modulators of the CB1 receptor and as such are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, particularly to opiates, alcohol, marijuana, and nicotine. The compounds are also useful for the treatment of obesity or eating disorders associated with excessive food intake and complications associated therewith. The compounds are also useful for the treatment of constipation and chronic intestinal pseudo-obstruction. The compounds are also useful for the treatment of cirrhosis of the liver. The compounds are also useful for the treatment of asthma.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The administration of the compound of structural formula I in order to practice the present methods of therapy is carried out by administering an effective amount of the compound of structural formula I to the patient in need of such treatment or prophylaxis. The need for a prophylactic administration according to the methods of the present invention is determined via the use of well known risk factors. The effective amount of an individual compound is determined, in the final analysis, by the physician in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration other drugs and treatments which the patient may concomitantly require, and other factors in the physician's judgment.

The utilities of the present compounds in these diseases or disorders may be demonstrated in animal disease models that have been reported in the literature. The following are examples of such animal disease models: a) suppression of food intake and resultant weight loss in rats (Life Sciences 1998, 63, 113-117); b) reduction of sweet food intake in marmosets (Behavioural Pharm. 1998, 9, 179-181);

c) reduction of sucrose and ethanol intake in mice (Psychopharm. 1997, 132, 104-106); d) increased motor activity and place conditioning in rats (Psychopharm. 1998, 135, 324-332; Psychopharmacol 2000, 151: 25-30); e) spontaneous locomotor activity in mice (J. Pharm. Exp. Ther. 1996, 277, 586-594); f) reduction in opiate self-administration in mice (Sci. 1999, 283, 401-404); g) bronchial hyperresponsiveness in sheep and guinea pigs as models for the various phases of asthma (for example, see W. M. Abraham et al., "α_4-Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep." J. Clin. Invest. 93, 776 (1993) and A. A. Y. Milne and P. P. Piper, "Role of VLA-4 integrin in leucocyte recruitment and bronchial hyperresponsiveness in the gunea-pig." Eur. J. Pharmacol., 282, 243 (1995)); h) mediation of the vasodilated state in advanced liver cirrhosis induced by carbon tetrachloride (Nature Medicine, 2001, 7 (7), 827-832); i) amitriptyline-induced constipation in cynomolgus monkeys is beneficial for the evaluation of laxatives (Biol. Pharm. Bulletin (Japan), 2000, 23(5), 657-9); j) neuropathology of paediatric chronic intestinal pseudo-obstruction and animal models related to the neuropathology of paediatric chronic intestinal pseudo-obstruction (Journal of Pathology (England), 2001, 194 (3), 277-88).

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of Formula I per kg of body weight per day and for preventive use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 1000 mg of a compound of Formula I per day, preferably from about 0.1 mg to about 10 mg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 0.01

to 1,000 mg, preferably 0.01, 0.05, 0.1, 0.5, 1, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 100, 250, 500, 750 or 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In particular, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be

conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulizers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which may be formulated as a dry powder of a compound of Formula I with or without additional excipients.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, solutions, ointments, gels, lotions, dusting powders, and the like. The topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.005% to 5% by weight of the active compound in admixture with a pharmaceutically acceptable vehicle. Transdermal skin patches useful for administering the compounds of the present inveniton include those well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case

solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules (including timed release and sustained release formulations), pills, cachets, powders, granules or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion, incluidng elixirs, tinctures, solutions, suspensions, syrups and emulsions. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from 0.01 to 1,000 mg, particularly 0.01, 0.05, 0.1, 0.5, 1, 2.5, 3, 5, 6, 10, 15, 25, 50, 75, 100, 125, 150, 175, 180, 200, 225, 500, 750 and 1,000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated, and each cachet or capsule contains from about 0.01 to 1,000 mg, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 3, 5, 6, 10, 15, 25, 50, 75, 100, 125, 150, 175, 180, 200, 225, 500, 750 and 1,000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Additional suitable means of administration of the compounds of the present invention include injection, intravenous bolus or infusion, intraperitoneal, subcutaneous, intramuscular and topical, with or without occlusion.

Exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Also exemplifying the invention is a pharmaceutical composition made by

combining any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

The dose may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, based on the properties of the individual compound selected for administration, the dose may be administered less frequently, e.g., weekly, twice weekly, monthly, etc. The unit dosage will, of course, be correspondingly larger for the less frequent administration.

When administered via intranasal routes, transdermal routes, by rectal or vaginal suppositories, or through a continual intravenous solution, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/mL
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0

Water for injection to a total volume of 1 mL

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	mg/capsule
Compound of Formula I	25

Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Aerosol	Per canister
Compound of Formula I	24 mg
Lecithin, NF Liq. Conc.	1.2 mg
Trichlorofluoromethane, NF	4.025 g
Dichlorodifluoromethane, NF	12.15 g

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I include, but are not limited to: antipsychotic agents, cognition enhancing agents, anti-migraine agents, anti-asthmatic agents, antiinflammatory agents, axiolytics, anti-Parkinson's agents, anti-epileptics, anorectic agents, and serotonin reuptake inhibitors, and other anti-obesity agents which may be administered separately or in the same pharmaceutical compositions.

It will be appreciated that for the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders, a compound of the present invention may be used in conjunction with other anorectic agents.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of an anorectic agent, such that together they give effective relief.

"Obesity" is a condition in which there is an excess of body fat. The operational definition of obesity is based on the Body Mass Index (BMI), which is calculated as body weight per height in meters squared (kg/m^2). "Obesity" refers to a condition whereby an otherwise healthy subject has a Body Mass Index (BMI) greater than or equal to 30 kg/m^2, or a condition whereby a subject with at least one co-morbidity has a BMI greater than or equal to 27 kg/m^2. An "obese subject" is an otherwise healthy subject with a Body Mass Index (BMI) greater than or equal to 30 kg/m^2 or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m^2. A "subject at risk for obesity" is an otherwise healthy subject with a BMI of 25 kg/m^2 to less than 30 kg/m^2 or a subject with at least one co-morbidity with a BMI of 25 kg/m^2 to less than 27 kg/m^2.

The increased risks associated with obesity occur at a lower Body Mass Index (BMI) in Asians. In Asian countries, including Japan, "obesity" refers to a condition whereby a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, has a BMI greater than or equal to 25 kg/m^2. In Asian countries, including Japan, an "obese subject" refers to a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, with a BMI greater than or equal to 25 kg/m^2. In Asian countries, a "subject at risk for obesity" is a subject with a BMI of greater than 23 kg/m^2 to less than 25 kg/m^2.

As used herein, the term "obesity" is meant to encompass all of the above definitions of obesity.

Obesity-induced or obesity-related co-morbidities include, but are not limited to, diabetes, non-insulin dependent diabetes mellitus - type 2, impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris sleep apnea syndrome, Pickwickian syndrome, fatty liver; cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, and infertility. In particular, co-morbidities include: hypertension, hyperlipidemia, dyslipidemia, glucose intolerance, cardiovascular disease, sleep apnea, diabetes mellitus, and other obesity-related conditions.

"Treatment" (of obesity and obesity-related disorders) refers to the administration of the compounds or compositions of the present invention to reduce or

maintain the body weight of an obese subject. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject's body weight immediately before the administration of the compounds or compositions of the present invention. Another outcome of treatment may be preventing regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate; and in weight reduction in patients in need thereof. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from weight loss.

"Prevention" (of obesity and obesity-related disorders) refers to the administration of the compounds or compositions of the present invention to reduce or maintain the body weight of a subject at risk for obesity. One outcome of prevention may be reducing the body weight of a subject at risk for obesity relative to that subject's body weight immediately before the administration of the compounds or compositions of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk for obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk for obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

Obesity-related disorders are associated with, caused by, or result from obesity. Examples of obesity-related disorders include overeating and bulimia, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer,

osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia. Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, sexual and reproductive dysfunction, such as infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer. The compositions of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy.

The term "diabetes," as used herein, includes both insulin-dependent diabetes mellitus (i.e., IDDM, also known as type I diabetes) and non-insulin-dependent diabetes mellitus (i.e., NIDDM, also known as Type II diabetes. Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes (i.e., non-insulin-dependent diabetes mellitus), often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese. The compounds and compositions of the present invention are useful for treating both Type I and Type II diabetes. The compounds and compositions are especially effective for treating Type II diabetes. The compounds and compositions of the present invention are also useful for treating and/or preventing gestational diabetes mellitus.

As used herein, the term "substance abuse disorders" includes substance dependence or abuse with or without physiological dependence. The substances associated with these disorders are: alcohol, amphetamines (or amphetamine-like substances), caffeine, cannabis, cocaine, hallucinogens, inhalants, marijuana, nicotine, opioids, phencyclidine (or phencyclidine-like compounds),

sedative-hypnotics or benzodiazepines, and other (or unknown) substances and combinations of all of the above.

In particular, the term "substance abuse disorders" includes drug withdrawal disorders such as alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances. It will be appreciated that reference to treatment of nicotine withdrawal includes the treatment of symptoms associated with smoking cessation.

Other "substance abuse disorders" include substance-induced anxiety disorder with onset during withdrawal; substance-induced mood disorder with onset during withdrawal; and substance-induced sleep disorder with onset during withdrawal.

It will be appreciated that a combination of a conventional antipsychotic drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of mania. Such a combination would be expected to provide for a rapid onset of action to treat a manic episode thereby enabling prescription on an "as needed basis". Furthermore, such a combination may enable a lower dose of the antispychotic agent to be used without compromising the efficacy of the antipsychotic agent, thereby minimizing the risk of adverse side-effects. A yet further advantage of such a combination is that, due to the action of the CB1 receptor modulator, adverse side-effects caused by the antipsychotic agent such as acute dystonias, dyskinesias, akathesia and tremor may be reduced or prevented.

The present invention also provides a method for the treatment or prevention of mania, which method comprises administration to a patient in need of such treatment or at risk of developing mania of an amount of a CB1 receptor modulator and an amount of an antipsychotic agent, such that together they give effective relief.

It will be appreciated that the CB1 receptor modulator and the antipsychotic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of mania.

It will be appreciated that when using a combination of the present invention, the CB1 receptor modulator and the antipsychotic agent may be in the same

pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms which are taken simultaneously. The term "combination" also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, the antipsychotic agent may be administered as a tablet and then, within a reasonable period of time, the CB1 receptor modulator may be administered either as an oral dosage form such as a tablet or a fast-dissolving oral dosage form. By a "fast-dissolving oral formulation" is meant, an oral delivery form which when placed on the tongue of a patient, dissolves within about 10 seconds.

It will be appreciated that a combination of a conventional antipsychotic drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of schizophrenic disorders. Such a combination would be expected to provide for a rapid onset of action to treat schizophrenic symptoms thereby enabling prescription on an "as needed basis". Furthermore, such a combination may enable a lower dose of the CNS agent to be used without compromising the efficacy of the antipsychotic agent, thereby minimizing the risk of adverse side-effects. A yet further advantage of such a combination is that, due to the action of the CB1 receptor modulator, adverse side-effects caused by the antipsychotic agent such as acute dystonias, dyskinesias, akathesia and tremor may be reduced or prevented.

It will be appreciated that a combination of a conventional anti-asthmatic drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of asthma.

Thus, according to a further aspect of the present invention there is provided the use of a CB1 receptor modulator and an anti-asthmatic agent for the manufacture of a medicament for the treatment or prevention of asthma.

The present invention also provides a method for the treatment or prevention of asthma, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of an anti-asthmatic agent, such that together they give effective relief.

The method of treatment of this invention comprises a method of modulating the CB1 receptor and treating CB1 receptor mediated diseases by administering to a patient in need of such treatment a non-toxic therapeutically

effective amount of a compound of this invention that selectively antagonizes the CB1 receptor in preference to the other CB or G-protein coupled receptors.

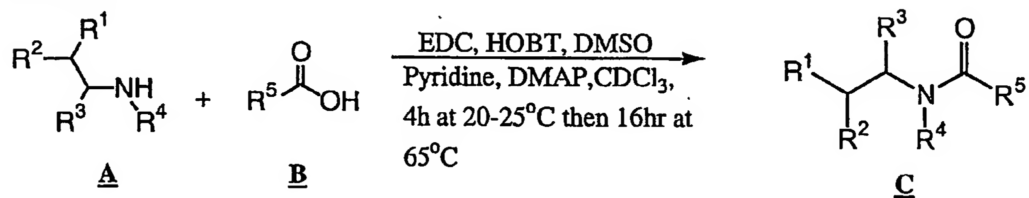
The term "therapeutically effective amount" means the amount the compound of structural formula I that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disorder being treated. The novel methods of treatment of this invention are for disorders known to those skilled in the art. The term “mammal” includes humans.

Abbreviations used in the following Schemes and Examples:

aq.: aqueous; API-ES: atmospheric pressure ionization-electrospray (mass spectrum term); DMF: dimethylformamide; DMSO: dimethylsulfoxide; EDC: 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; EPA: ethylene polyacrylamide (a plastic); EtOAc: ethyl acetate; h: hours; Hex: hexane; HOBt: 1-hydroxybenzo-triazole; HPLC: high pressure liquid chromatography; HPLC/MS: high pressure liquid chromatography/mass spectrum; *in vacuo:* rotoevaporation; IPAC: isopropyl acetate; KHMDS: potassium hexamethyldisilazide; LC: Liquid chromatography; LC/MS, LC-MS: liquid chromatography-mass spectrum; M: molar; Me: methyl; MeOH: methanol; mmol: millimole; MS or ms: mass spectrum; N: normal; NaHMDS: sodium hexamethyldisilazide; NMR: nuclear magnetic resonance; PyBOP: (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; R_t: retention time; rt or RT: room temperature; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TLC: thin layer chromatography.

Compounds of the present invention may be prepared by procedures illustrated in the accompanying scheme and examples.

Scheme 1.

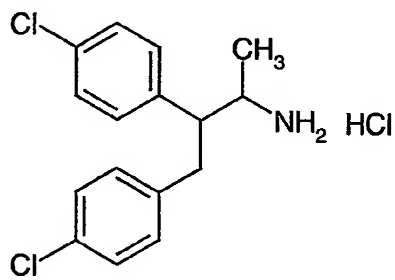


In Scheme 1, an appropriately substituted amine A is reacted with a carboxylic acid B under standard amide bond forming conditions to afford the arylamide C. In order to illustrate the invention, the following examples are included. These examples do not limit the invention. They are only meant to suggest

a method of reducing the invention to practice. Those skilled in the art may find other methods of practicing the invention which are readily apparent to them. However, those methods are also deemed to be within the scope of this invention.

General Procedures. The LC/MS analyses were preformed using a MICROMASS ZMD mass spectrometer coupled to an AGILENT 1100 Series HPLC utilizing a YMC ODS-A 4.6 x 50 mm column eluting at 2.5 mL/min with a solvent gradient of 10 to 95% B over 4.5 min, followed by 0.5 min at 95% B: solvent A = 0.06% TFA in water; solvent B = 0.05% TFA in acetonitrile. ^{1}H-NMR spectra were obtained on a 500 MHz VARIAN Spectrometer in $CDCl_3$ or CD_3OD as indicated and chemical shifts are reported as δ using the solvent peak as reference and coupling constants are reported in hertz (Hz).

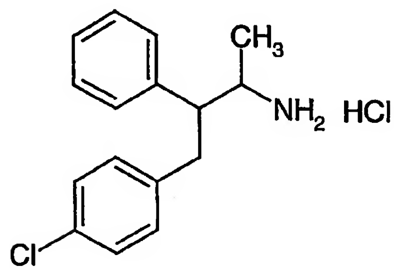
REFERENCE EXAMPLE 1



N-[2,3-Bis(4-chlorophenyl)-1-methylpropyl]-amine hydrochloride

The preparation of the two diastereomers (alpha and beta) of *N*-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-amine hydrochloride salt has been disclosed (Schultz, E.M, *et al. J. Med Chem.* 1967, *10*, 717). Diastereomer α: LC-MS: calculated for $C_{16}H_{17}Cl_2N$ 293, observed m/e 294 $(M + H)^+$ (retention time 2.5 min). Diastereomer β: LC-MS: calculated for $C_{16}H_{17}Cl_2N$ 293, observed m/e 294 $(M + H)^+$ (retention time 2.2 min).

REFERENCE EXAMPLE 2



2-Amino-4-(4-chlorophenyl)-3-phenylbutane hydrochloride salt

The titled compound was prepared by the procedure described in Reference Example 1.

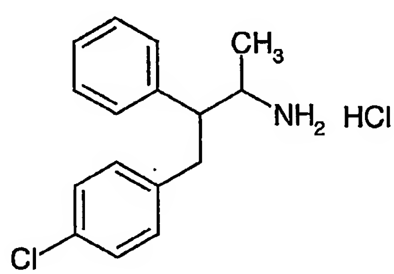
Diastereomer α:

LC-MS: calculated for $C_{16}H_{18}ClN$ 259, observed m/e 260 $(M + H)^+$ (2.3 min).

Diastereomer β:

LC-MS: calculated for $C_{16}H_{18}ClN$ 259, observed m/e 260 $(M + H)^+$ (2.2 min).

REFERENCE EXAMPLE 3



N-[3-(4-Chlorophenyl)-2-phenyl-1-methylpropyl]-amine hydrochloride (Diastereomer α)

Step A 3-(4-Chlorophenyl)-2-phenylpropanoic acid, methyl ester.

To a solution of methyl phenylacetate (12 g, 80 mmol) and 4-chlorobenzyl bromide (16 g, 80 mmol) in 250 mLanhydrous THF at –78°C was added sodium hexamethyldisilazide (1 M in THF, 80 mL, 80 mmol) (potassium hexamethyldisilazide in toluene may be used with similar results). The reaction was allowed to warm to room temperature overnight. The volatile materials were

removed on a rotary evaporator, and the resulting mixture was partitioned between saturated ammonium chloride (200 mL) and EtOAc (200 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give the title compound

^{1}H NMR (500 MHz, CD_3OD): δ 7.36-7.10 (m, 9H), 3.81 (dd, 1H), 3.52 (s, 3H), 3.36 (dd, 1H), 3.02 (dd, 1H).

Step B <u>3-(4-Chlorophenyl)-2-phenylpropanoic acid.</u>

To a mixture of methyl 3-(4-chlorophenyl)-2-phenylpropionate (Step A, 20 g, 74 mmol) in acetonitrile (100 mL) and water (100 mL) was added lithium hydroxide monohydrate (8.8 g, 0.21 mol). After stirring at room temperature for 3 days, the volatile materials were removed by concentrating on a rotary evaporator and the residue was partitioned between water (300 mL) and hexane/ether (1:1, 200 mL). The water layer was separated, acidified to pH = 2-3, and extracted with EtOAc (2 x 200 mL) The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.34-7.10 (m, 9H), 3.82 (dd, 1H), 3.36 (dd, 1H) , 2.98 (dd, 1H).

Step C <u>*N*-Methoxy-*N*-methyl-3-(4-chlorophenyl)-2-phenylpropanamide.</u>

To a solution of 3-(4-chlorophenyl)-2-phenylpropionic acid (Step B, 14 g, 55 mmol) in CH_2Cl_2 (125 mL) at 0°C was added dimethyl formamide (50 μL) and oxalyl chloride (14 g, 0.11 mol) dropwise. The reaction was allowed to warm to room temperature overnight and concentrated to dryness to give the crude acyl chloride, which was used without further purification. Thus, to a solution of the acyl chloride in CH_2Cl_2 (250 mL) was added *N*-methoxy-*N*-methylamine hydrochloride (11 g, 0.11 mol) and triethyl amine (dried over activated molecular sieves, 30 mL, 0.22 mol) at 0°C. After stirring at room temperature for 4 h, the reaction mixture was diluted with ether (500 mL) and successively washed with water, dilute aqueous sodium hydrogen sulfate and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to give the crude product, which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 7.4-7.1 (m, 9H), 4.38 (br, 1H), 3.48 (s, 3H), 3.35 (dd, 1H), 3.10 (s, 3H), 2.92 (dd, 1H); LC-MS: m/e 304 (3.6 min).

Step D <u>4-(4-Chlorophenyl)-3-phenyl-2-butanone.</u>

To a solution of *N*-methoxy-*N*-methyl-3-(4-chlorophenyl)-2-phenylpropanamide (Step C, 16 g, 53 mmol, dried by azeotroping with toluene) in anhydrous THF (200 mL) at 0°C was added methylmagnesium bromide (3 M in ether, 35 mL, 0.11 mol).

After stirring at 0°C for 2 h, the reaction was quenched with MeOH (5 mL) and 2 M hydrochloric acid (50 mL). The volatile materials were removed by concentrating on a rotary evaporator and the residue partitioned between saturated ammonium chloride (200 mL) and ether (200 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 x 200 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to give the title compound, which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 7.45-7.02 (m, 9H), 4.08 (dd, 1H), 3.34 (dd, 1H), 2.90 (dd, 1H), 2.03 (s, 3H).

Step E 4-(4-Chlorophenyl)-3-phenyl-2-butanol.

To a solution of 4-(4-chlorophenyl)-3-phenyl-2-butanone (Step D, 13 g, 50 mmol) in MeOH (100 mL) at 0 °C was added sodium borohydride (3.8 g, 100 mmol). After stirring at 0°C for 30 min, the reaction was quenched by addition of 2 M hydrochloric acid (50 mL). The volatile materials were removed by concentrating on a rotary evaporator and the residue partitioned between water (100 mL) and EtOAc (200 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness to give the crude product, which was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to afford the pure faster eluting isomer and a mixture containing both the faster eluting isomer and the slower eluting isomer.

Faster eluting isomer: ^{1}H NMR (500 MHz, CD_3OD): δ 7.25-7.00 (m, 9H), 4.00 (m, 1H), 3.15 (m, 1H), 2.97 (m, 1H), 2.85 (m, 1H), 1.10 (d, 3H).

Step F 4-(4-Chlorophenyl)-2-methanesulfonyloxy-3-phenylbutane.

To a solution of 4-(4-chlorophenyl)-3-phenyl-2-butanol (Step E, faster eluting isomer, 9.0 g, 34 mmol) in EtOAc (100 mL) at 0°C was added triethyl amine (dried over activated molecular sieves, 5.8 mL. 42 mmol) and methanesulfonyl chloride (3.0 mL, 38 mmol). After stirring at 0°C for 30 min, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (100 mL). After stirring at room temperature for 1 h, the organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to give the title compound, which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 7.3-7.0 (m, 9H), 5.05 (m, 1H), 3.2-3.0 (m, 3H), 2.80 (s, 3H), 1.40 (d, 3H).

Step G 2-Azido-4-(4-chlorophenyl)-3-phenylbutane.

To a solution of 4-(4-chlorophenyl)-2-methanesulfonyloxy-3-phenylbutane (Step F, 12 g, 34 mmol) in DMF (50 mL) was added sodium azide (11 g, 0.17 mol). After stirring at 120°C for 1 h, the reaction mixture was poured into water (200 mL), and the product was extracted with ether (2 x 100 mL). The combined organic extracts were washed with water, dried over $MgSO_4$, filtered and concentrated to dryness, and the residue was purified on a silica gel column eluting with hexane to give the title compound.

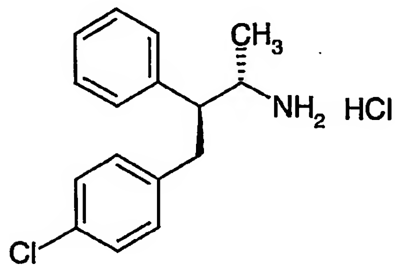
Step H 2-(*N-tert*-Butoxycarbonyl)amino-4-(4-chlorophenyl)-3-phenylbutane

To a solution of 2-azido-4-(4-chlorophenyl)-3-phenylbutane (Step G, 7.0 g, 24 mmol) in EtOAc (150 mL) was added di(*tert*-butyl) dicarbonate (8.0 g, 37 mmol) and platinum dioxide (0.50 g, 2.2 mmol). The mixture was degassed and filled with hydrogen with a balloon. After stirring for 1 day, the reaction mixture was filtered through CELITE diatomaceous earth, and the filtrate was concentrated to give the crude product, which was contaminated with some unreacted di(*tert*-butyl) dicarbonate. ^{1}H NMR (500 MHz, CD_3OD): δ 7.25-6.88 (m, 9H), 3.89 (m, 1H), 3.20 (m, 1H), 2.86-2.77 (m, 2H), 1.54 (s, 9H), 0.92 (d, 3H).

Step I N-[3-(4-Chlorophenyl)-2-phenyl-1-methylpropyl]-amine hydrochloride (Diastereomer α).

2-(*N-tert*-butoxycarbonyl)amino-4-(4-chlorophenyl)-3-phenylbutane (Step H, 7.0 g, 24 mmol) was treated with a saturated solution of hydrogen chloride in EtOAc (100 mL) at room temperature for 30 min (4 M hydrogen chloride in dioxane may be used with similar results). The mixture was concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.35-6.98 (m, 9H), 3.62 (m, 1H), 3.20 (dd, 1H), 3.05 (m, 1H), 2.98 (dd, 1H), 1.19 (d, 3H). LC-MS: m/e 260 $(M + H)^+$ (2.3 min).

REFERENCE EXAMPLE 4



<u>*N*-[3-(4-Chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-amine hydrochloride</u>

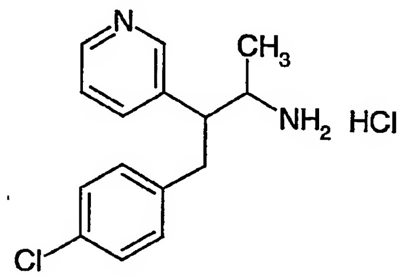
Step A <u>4-(4-Chlorophenyl)-3(S)-phenyl-2(R)-butanol</u>.

A sample of magnesium (20 g, 0.82 mol) was activated by stirring under nitrogen for 12 h, and anhydrous ether (100 mL) was added to cover the solid material. The mixture was cooled to 0°C, and was added 4-chlorobenzyl chloride (40 g, 0.25 mmol) in 400 mL anhydrous ether dropwise. After stirring at room temperature for 1 h, a sample of the above solution (32 mL) was added to (1*R*,2*R*)-1-phenylpropylene oxide (1.0 g, 7.5 mmol) in 100 mL ether at 0°C via syringe. After stirring at 0°C for 2 h, the reaction was quenched by addition of saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer extracted with ether (2 x 100 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with hexane to 15% EtOAc in hexane to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 7.28-7.02 (m, 9H), 4.01 (m, 1H), 3.14 (dd, 1H), 2.97 (dd, 1H), 2.85 (m, 1H), 1.12 (d, 3H).

Step B <u>*N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-amine, hydrochloride</u>

The product of Step A (4-(4-chlorophenyl)-3(S)-phenyl-2(R)-butanol, 1.8 g, 7.0 mmol) was converted to the title compound following the steps described in Reference Example 3, Steps F-I, except hydrogen chloride in dioxane (4 M) was used in place of hydrogen chloride in EtOAc. ^1H NMR (500 MHz, CD_3OD): δ 7.35-6.98 (m, 9H), 3.62 (m, 1H), 3.20 (dd, 1H), 3.05 (m, 1H), 2.98 (dd, 1H), 1.19 (d, 3H). LC-MS: m/e 260 $(M + H)^+$ (2.3 min).

REFERENCE EXAMPLE 5



N-[3-(4-chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-amine, hydrochloride (mixture of diastereomers α/β 10:1)

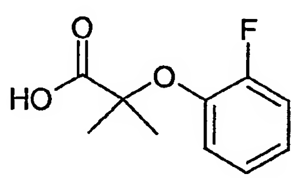
Step A 4-(4-Chlorophenyl)-3-pyridyl-2-butanone.

To a solution of 3-pyridylacetone hydrochloride (Wibaud, van der V. *Recl. Trav. Chim. Pays-Bas.* 1952, *71*, 798) (10 g, 58 mmol) and 4-chlorobenzyl chloride (9.1 g, 58 mmol) in 100 mL CH_2Cl_2 at –78°C was added cesium hydroxide monohydrate (39 g, 0.23 mol) and tetrabutyl ammonium iodide (1 g). The reaction was allowed to warm to room temperature overnight, and the resulting mixture was partitioned between brine (100 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.42 (d, 1H), 8.34 (d, 1H), 7.72 (d, 1H), 7.40 (dd, 1H), 7.18 (d, 2H), 7.06 (d, 1H), 4.23 (dd, 1H), 3.38 (dd, 1H), 2.95 (dd, 1H), 2.10 (s, 3H). LC-MS: m/e 260 $(M + H)^+$ (1.9 min).

Step B N-[3-(4-chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-amine, hydrochloride (mixture of diastereomers α/β 10:1).

The product of Step A (4-(4-chlorophenyl)-3-pyridyl-2-butanone) (14 g, 57 mmol) was converted to the title compound following the procedure described in Reference Example 3, Steps E-I. LC-MS: m/e 261 $(M + H)^+$ (1.2 min).

REFERENCE EXAMPLE 6



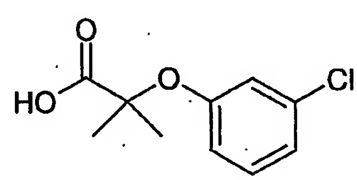
2-(2-Fluorophenyloxy)-2-methylpropionic acid

Step A 2-(2-Fluorophenyloxy)-2-methylpropionic acid

To a solution of 2-fluorophenol (2.0 g, 18 mmol) and 1,1,1-trichloro-2-methyl-2-propanol (7.9 g, 45 mmol) in acetone (100 mL) was added sodium hydroxide (7.1 g, 0.18 mol), and an ice-water bath was periodically applied to maintain a gentle reflux. After the reflux subsided, the reaction was stirred for one additional hour. The volatile materials were removed on a rotary evaporator, and the residue partitioned between ether (100 mL), hexane (100mL) and water (200 mL). The aqueous layer was separated and acidified with concentrated hydrochloric acid (pH = 2), and extracted with ether (3 x 100 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to give the title compound, which was used without further purification. ^1H NMR (500 MHz, CD_3OD): δ 7.15-7.05 (m, 4H), 1.56 (s, 6H). LC-MS: m/e 199 $(M + 1)^+$ (2.3 min).

The acids of Reference Examples 7 and 8 were prepared following the procedures described for Reference Example 6 substituting 2-fluorophenol with appropriately substituted phenols.

REFERENCE EXAMPLE 7

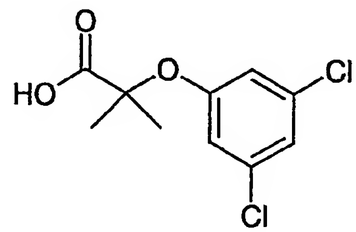


2-(3-Chlorophenyloxy)-2-methylpropionic acid

^1H NMR (500 MHz, CD_3OD): δ 7.23 (t, 1H), 7.00 (dd, 1H), 6.93 (t, 1H), 6.84 (dd, 1H), 1.59 (s, 6H).

LC-MS: m/e 215 $(M + 1)^+$, (2.7 min).

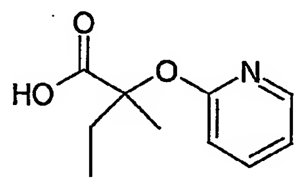
REFERENCE EXAMPLE 8



2-(3,5-Dichlorophenyloxy)-2-methylpropionic acid

^{1}H NMR (500 MHz, CD_3OD): δ 7.05 (t, 1H), 6.84 (d, 2H), 1.60 (s, 6H).

REFERENCE EXAMPLE 9



2-(2-Pyridyloxy)-2-methylbutanoic acid.

Step A Benzyl 2-(2-Pyridyloxy)propionate

To a mixture of 2-hydroxypyridine (2.9 g, 30 mmol), benzyl lactate (5.0 g, 21 mmol) and triphenylphosphine (12 g, 47 mmol) in 100 mL CH_2Cl_2 was added diethylazodicarboxylate (7.8 mL, 45 mmol) at 0°C. The reaction was allowed to warm to room temperature for 4 h. The resulting mixture was diluted with hexane (100 mL) and concentrated with 20 g silica gel. The material was loaded onto a silica gel column, which was eluted with 10% EtOAc in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.00 (dd, 1H), 7.68 (ddd, 1H), 7.36-7.28 (m, 5 H), 6.94 (dd, 1H), 6.84 (dd, 1H), 5.30 (q, 1H), 5.18 (s, 2H), 1.59 (d, 3H). LC-MS: m/e 258 $(M + H)^+$ (3.3 min).

Step B Benzyl 2-(2-Pyridyloxy)-2-methylbutanoate.

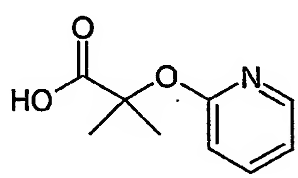
To a solution of benzyl 2-(2-pyridyloxy)propionate (1.6 g, 6.2 mmol) and ethyl iodide (1.5 mL, 25 mmol) in 10 mLanhydrous THF at –78°C was added sodium hexamethyldisilazide (1 M in THF, 9.3 mL, 9.3 mmol) (potassium hexamethyldisilazide in toluene may be used with similar results). The reaction was allowed to warm to room temperature over 2 h and was partitioned between saturated ammonium chloride (100 mL) and EtOAc (100 mL). The organic layer was separated

and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.87 (dd, 1H), 7.63 (ddd, 1H), 7.27 (m, 3H), 7.18. (m, 2H), 6.85 (dd, 1H), 6.74 (dd, 1H), 5.08 (ABq, 2H), 2.13 (m, 1H), 1.94 (m, 1H), 1.65 (s, 3H), 0.95 (t, 3H). LC-MS: m/e 286 $(M + H)^+$ (3.8 min).

Step C 2-(2-Pyridyloxy)-2-methylbutanoic Acid

A mixture of benzyl 2-(2-pyridyloxy)-2-methylbutanoate (1.6 g, 5.5 mmol) and 10% palladium on carbon (50 mg) in 50 mL MeOH was degassed and filled with hydrogen using a balloon. After stirring at room temperature overnight, the reaction mixture was filtered through CELITE diatomaceous earth and washed with MeOH (20 mL), and the filtrate was concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.03 (dd, 1H), 7.64 (ddd, 1H), 6.89 (dd, 1H), 6.76 (dd, 1H), 2.14 (m, 1H), 1.94 (m, 1H), 1.64 (s, 3H), 0.99 (t, 3H). LC-MS: m/e 196 $(M + H)^+$ (1.8 min).

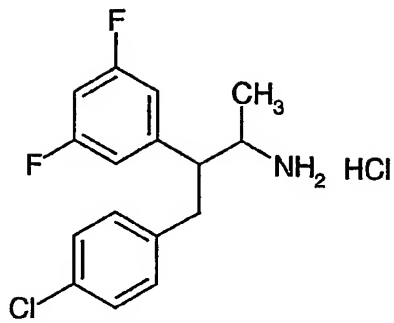
REFERENCE EXAMPLE 10



2-(2-Pyridyloxy)-2-methylpropionic Acid

The title compound was prepared following the procedures described for Reference Example 9 substituting ethyl iodide and sodium hexamethyldisilazide with methyl iodide and potassium hexamethyldisilazide respectively at Step B. ^{1}H NMR (500 MHz, CD_3OD): δ 8.04 (dd, 1H), 7.64 (ddd, 1H), 6.89 (dd, 1H), 6.76 (dd, 1H), 1.66 (s, 6H). LC-MS: m/e 182 $(M + H)^+$ (1.5 min).

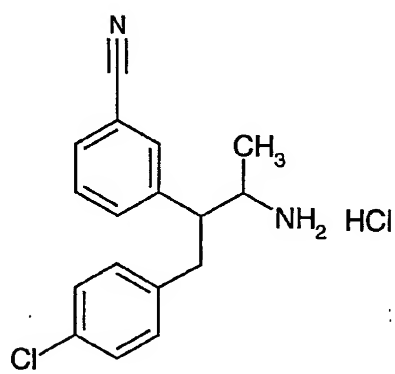
REFERENCE EXAMPLE 11



N-[3-(4-Chlorophenyl)-2-(3,5-difluorophenyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

The title compounds was prepared following the procedures described for Reference Example 3 substituting methyl phenylacetate with methyl 3,5-difluorophenylacetate (prepared from 3,5-difluorophenylacetic acid and trimethylsilyldiazomethane) at Step A and sodium borohydride in MeOH with lithium tri(*sec*-butylborohydride in THF at Step E. LC-MS: m/e 296 $(M + H)^+$ (2.39 min).

REFERENCE EXAMPLE 12



N-[3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

Step A 2-(*N-tert*-Butoxycarbonyl)amino-4-(4-chlorophenyl)-3-(3-cyanophenyl)butane

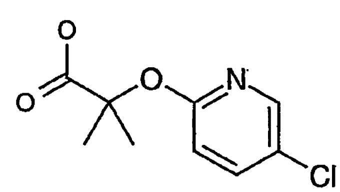
To a solution of 2-(*N-tert*-butoxycarbonyl)amino-3-bromophenyl-4-(4-chlorophenyl)butane (prepared according to the procedure of Reference Example 3, Step H, 1.0 g, 2.3 mmol) in 5 mL DMF was added zinc cyanide (0.16 g, 1.4 mmol), tris(dibenzylidene-acetone)dipalladium chloroform complex (3.0 mg, 2.8 μmol), 1,1'-

bis(diphenylp-hosphino)ferrocene (5.0 mg, 9.0 µmol) and water (0.1 mL). After heating at 120°C for 6 h under nitrogen, another batch of zinc cyanide (0.16 g, 1.4 mmol), tris(dibenzylideneacetone)dipalladium chloroform complex (5.0 mg, 4.8 µmol), 1,1'-bis(diphenylphosphino)ferrocene (5.0 mg, 9.0 µmol) and water (0.05 mL) was added, and heating was continued for another 18 h. After cooling to room temperature, the resulting mixture was partitioned between water (50 mL) and ether (50 mL). The organic layer was separated and the aqueous layer extracted with ether (2 x 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated, and the residue was purified by flash column chromatography on silica gel eluted with 20% EtOAc in hexane to afford the title compound. ^1H NMR (400 MHz, CD_3OD): δ 7.6-7.3 (m, 4H), 7.10 (d, 2H), 6.92 (d, 2H), 3.88 (m, 1H), 3.20 (m, 1H), 2.97 (m, 1H), 1.82 (m, 1H), 1.45 (s, 9H), 0.94 (d, 3H). LC-MS: m/e 385 $(M + H)^+$ (3.9 min).

Step B <u>*N*-[3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)</u>

The title compound was prepared following the procedure described for Reference Example 3, Step I. LC-MS: m/e 285 $(M + H)^+$ (2.2 min).

REFERENCE EXAMPLE 13



<u>2-Methyl-2-(5-chloro-2-pyridyloxy)propionic acid</u>

Step A <u>Ethyl 2-Methyl-2-(5-chloro-2-pyridyloxy)propionate</u>

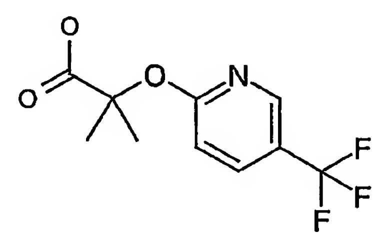
A mixture of 5-chloro-2-hydroxypyridine (5.0 g, 39 mmol), ethyl 2-bromoisobutyrate (5.7 mL, 39 mmol) and cesium carbonate (25 g, 77 mmol) in 50 mL acetonitrile was heated at 50°C overnight. The volatile materials were removed by concentrating on a rotary evaporator, and the residue was partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 5% EtOAc in hexane to give

the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.99 (d, 1H), 7.67 (dd, 1H), 6.68 (d, 1H), 4.13 (q, 2H), 1.64 (s, 6H), 1.14 (t, 3H). LC-MS: m/e 244 $(M + H)^+$ (3.41 min).

Step B <u>2-Methyl-2-(5-chloro-2-pyridyloxy)propionic Acid</u>

A mixture of ethyl 2-methyl-2-(5-chloro-2-pyridyloxy)propionate and sodium hydroxide (0.85 g, 21 mmol) in 15 mL acetonitrile and 15 mL water was heated at 50°C overnight. The volatile materials were removed by concentrating on a rotary evaporator, and the residue was partitioned between 2 M hydrochloric acid (100 mL) and ether (100 mL). The organic layer was separated and washed with water (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.02 (d, 1H), 7.65 (dd, 1H), 6.77 (d, 1H), 1.62 (s, 6H). LC-MS: m/e 216 $(M + H)^+$ (2.33 min).

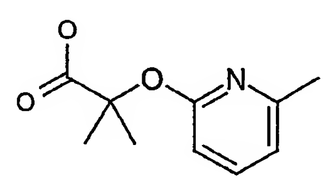
REFERENCE EXAMPLE 14



<u>2-Methyl-2-(5-trifluoromethyl-2-pyridyloxy)propionic Acid</u>

The title compound was prepared following the procedures described for Reference Example 13 substituting 5-chloro-2-hydroxpyridine with 5-trifluoromethyl-2-hydroxpyridine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 8.38 (br s, 1H), 7.93 (dd, 1H), 7.13 (d, 1H), 1.70 (s, 6H). LC-MS: m/e 250 $(M + H)^+$ (2.6 min).

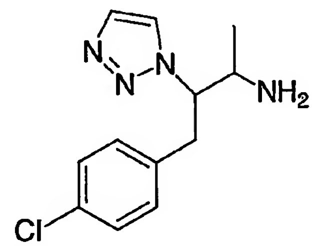
REFERENCE EXAMPLE 15



<u>2-Methyl-2-(6-methyl-2-pyridyloxy)propionic Acid</u>

The title compound was prepared following the procedures described for Reference Example 13 substituting 5-chloro-2-hydroxpyridine with 6-methyl-2-hydroxpyridine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 7.51 (t, 1H), 6.74 (d, 1H), 6.53 (d, 1H), 2.34 (s, 3H), 1.64 (s, 6H). LC-MS: m/e 196 $(M + H)^+$ (1.3 min).

REFERENCE EXAMPLE 16



2-Amino-3-(1-(1,2,3-triazolyl))-4-(4-chlorophenyl)butane:

Step A Benzyl 2-(1-(1,2,3-triazolyl))acetate:

A mixture of 1,2,3-triazole (2.07 g, 30 mmol), phenyl bromoacetate (6.9 g, 30 mmol), and diisopropylethylamine (5,1 mL, 30 mmol) in 40 mL CH_2Cl_2 was stirred overnight at room temperature. This mixture was then diluted with ether until no further precipitate formed. The solid was filtered and washed with ether. The filtrate was concentrated and the residue was purified on silica gel using 10% hexane in CH_2Cl_2 to give the title compound's isomer, benzyl 2-(2-(1,2,3-triazolyl)acetate as amorphous solid. Further elution with a solvent mixture containing equal amounts of ether and CH_2Cl_2 gave the title compound as amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$):δ 2.251(s, 2H0, 7.267-7.390(m, 5H), 7.723(s, 1H), 7.785(s,1H)

Step B 2-(1-(1,2,3-triazolyl))acetic acid:

Palladium hydroxide (20% on carbon, 800 mg) was added to a solution of benzyl 2-(1-(1,2,3-triazolyl))acetate (Step A, 8.68 g, 39.9 mmol) in 150 mL MeOH and the mixture was hydrogenated overnight on a Parr shaker under an atmosphere of hydrogen at room temperature and 45 psi. The catalyst was filtered through a bed of CELITE diatomaceous earth and washed with MeOH. The filtrate was concentrated to give a solid, which was dried in vacuo at 50°C for 36 h resulting in the title compound. ^{1}H NMR (400 MHz, CD_3OD):δ 5.3 (s, 2H), 7,75 (s, 1H0, 8.016 (s, 1H).

Step C N-Methoxy-N-methyl-2-(1-(1,2,3-triazolyl))acetamide:

Oxalyl chloride (0.95 mL, 11 mmol) was added dropwise to a suspension of 2-(1-1,2,3-triazolyl))acetic acid (Step B, 1.27 g, 10 mmol) in 10 mL CH_2Cl_2 containing

0.05 mL DMF. Vigorous effervescence was observed. This mixture was stirred at room temperature for 4 h and cooled to -78°C. A solution of N.O-dimethylhydroxylamine hydrochloride (1.2 g, 13 mmol) and diisopropylethyl amine (6.0 mL, 35 mmol) in 10 mL CH_2Cl_2 was added slowly over 3 min. The mixture was then allowed to warm to room temperature and stirred overnight . The reaction mixture was then diluted with ether until no additional precipitate appeared. The solid was filtered and washed with ether. The filtrate was concentrated and the residue was purified on silica gel using EtOAc as solvent to provide the title compound as amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$):δ 3.252 (s, 3H0, 3.812 (s, 3H), 5.379 (s, 2H), 7.753 & 7.761 (s's, 2H).

Step D N-Methoxy-N-methyl-3-(4-chlorophenyl)-2-(1-(1,2,3-triazolyl)) propionamide

Lithium hexamethyldisilazide (1molar in THF, 8.4 mL, 8.4 mmol) was added dropwise to a solution of N-methoxy-N-methyl-2-(1-(1,2,3-triazolyl))acetamide (Step C, 1.19 g, 7 mmol) in 15 mL THF at -78°C. After additional 30 min stirring, a solution of 4-chlorobenzyl bromide (1.65 g, 8 mmol) in 5 mL THF was added dropwise. The mixture was allowed to warm to room temperature and stirred 5.5 h. This mixture was purified on silica gel using 40% EtOAc in hexane to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$.): δ 3.186 (s, 3H), 3.234-3,267 (m, 1H), 3,453-3.506 (m, 1H), 3.582 (s, 3H), 6.145-6.188 (m, 1H), 7.048-7.279 (m, 4H), 7.726 (s, 1H), 7.954 (s, 1H).

Step E 2-Azido-3-(1-(1,2,3-triazolyl))-4-(4-chlorophenyl)butane:

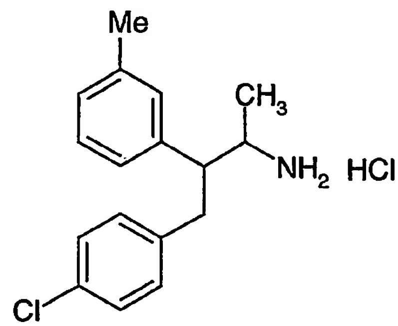
The product of Step D, N-methoxy-N-methyl-3-(4-chlorophenyl)-2-(1-(1,2,3-triazolyl)propionamide was converted to the title compound following the procedures described in Reference Example 3, Step D-G. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.219-1.246 (d's 3H), 3.253-4.754 (m, 4H0, 6.866-7.299 (d's, 4H), 7.313, 7.618, 7.63, & 7.706 (s's, 2H).

Step F 2-Amino-3-(1-(1,2,3-triazolyl))-4-(4-chlorophenyl)butane:

Platinum oxide (14 mg) was added to a solution of 2-azido-3-(1-(1,2,3-triazolyl))-4-(4-chlorophenyl)butane (Step E, 138 mg, 0.5 mmol) in 4 mL MeOH. This mixture was hydrogenated in an atmosphere of hydrogen using a hydrogen filled balloon for 3 h at room temperature. The catalyst was filtered through a bed of CELITE diatomaceous earth and washed with MeOH. The filtrate was concentrated to give the title compound as oil. ^{1}H NMR (400 MHz, $CDCl_3$):δ 1.085-1.174 (d's 3H), 3.220-

3.361 (m, 2H), 3.517-3.563 (m, 1H), 4.379-4.431 (m, 1H), 6.679-7.179 (d's, 4H), 7.297, 7.40, 7.592 & 7.607 (s's, 2H).

REFERENCE EXAMPLE 17



N-[3-(4-Chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

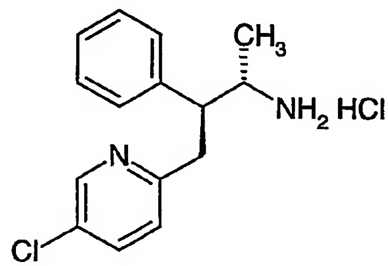
Step A 2-(*N-tert*-Butoxycarbonyl)amino-4-(4-chlorophenyl)-3-(3-methylphenyl)butane

A mixture of 2-(*N-tert*-butoxycarbonyl)amino-3-(3-bromophenyl)-4-(4-chlorophenyl)butane (Reference Example 3, Step H, 0.50 g, 1.1 mmol), tetramethyltin (0.41 g, 2.3 mmol), triphenylphosphine (0.12 g, 0.46 mmol), lithium chloride (0.38 g, 9.1 mmol) and dichlorobis(triphenylphosphine)palladium (0.12 g, 0.17 mmol) in 20 mL anhydrous DMF was heated at 100°C under nitrogen for 18 h. The reaction mixture was cooled to room temperature, and was partitioned between water (100 mL) and ether (100 mL). The organic layer was separated and the aqueous layer was extracted with ether (100 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to afford the title compound. ^{1}H NMR (400 MHz, CD_3OD): δ 7.2-6.8 (m, 8H), 3.84 (m, 1H), 3.16 (m, 1H), 2.80-2.68 (m, 2H), 2.24 (s, 3H), 1.45 (s, 9H), 0.86 (d, 3H). LC-MS: m/e 396 $(M + Na)^+$ (4.4 min).

Step B N-[3-(4-Chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

The title compound was prepared following the procedure described for Reference Example 3, Step I. LC-MS: m/e 274 $(M + H)^+$ (2.5 min).

REFERENCE EXAMPLE 18



N-[3-(5-Chloro-2-pyridyl)-2(S)-phenyl-1(S)-methylpropyl]amine hydrochloride (Diastereomer α)

Step A 5-Chloro-2-methylpyridine

A mixture of 2,5-dichloropyridine (15 g, 0.10 mol), tetramethyltin (15 mL, 0.11 mol), and dichlorobis(triphenylphosphine)palladium (2.0 g, 2.8 mmol) in 200 mL anhydrous DMF was heated at 110°C under nitrogen for 72 h. The reaction mixture was cooled to room temperature, and was poured into a saturated solution of potassium fluoride (200 mL). The resulting mixture was partitioned between water (500 mL) and ether (500 mL). The organic layer was separated and the aqueous layer was extracted with ether (200 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 2 to 10% ether in hexane to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.41 (d, 1H), 7.75 (dd, 1H), 7.30 (d, 1H), 2.53 (s, 3H).

Step B 4-(5-Chloro-2-pyridyl)-3(S)-phenyl-2(R)-butanol.

To a solution of 5-chloro-2-methylpyridine (Step A, 1.1 g, 8.7 mmol) in 15 mL anhydrous ether was added phenyl lithium (1.8 M in cyclohexane/ether, 7.2 mL, 13 mmol) at 0°C, and the reaction was stirred at room temperature for 30 min. The resulting mixture was cooled back to 0°C, and was added (1*R*,2*R*)-1-phenylpropylene oxide (2.3 g, 17 mmol), and the reaction was allowed to warm to room temperature overnight. The reaction mixture was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 10 to 40% EtOAc in hexane to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.28 (d, 1H), 7.59 (dd,

1H), 7.25-7.12 (m, 5H), 7.05 (d, 1H), 4.03 (m, 1H), 3.29 (dd, 1H), 3.19 (dd, 1H), 3.12 (m, 1H), 1.12 (d, 3H).

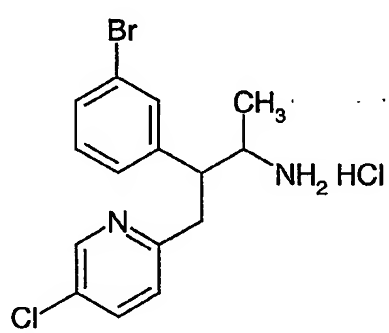
Step C 2(S)-Azido-4-(5-chloro-2-pyridyl)-3(S)-phenylbutane

To a mixture of 4-(5-chloro-2-pyridyl)-3-phenyl-2-butanol (Step B, 0.24 g, 0.92 mmol), triphenylphosphine (1.5 g, 1.4 mmol) and diphenylphosphoryl azide (0.30 mL, 1.4 mmol) in 5 mL anhydrous THF was added diethylazodicarboxylate (0.24 mL, 1.4 mmol). After stirring at room temperature overnight, the resulting mixture was concentrated with silica gel (10 g) and the residue was loaded onto a silica gel column. Elution with 5 to 15% EtOAc in hexane afforded the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.35 (d, 1H), 7.52 (dd, 1H), 7.25-7.05 (m, 5H), 6.95 (d, 1H), 3.81 (m, 1H), 3.48 (m, 1H), 3.15-3.05 (m, 2H), 1.14 (d, 3H).

Step D *N*-[3-(5-Chloro-2-pyridyl)-2(S)-phenyl-1(S)-methylpropyl]amine, hydrochloride

The product of Step C (0.20 g, 0.70 mmol) was converted to the title compound following the procedure described in Reference Example 3, Steps H-I, except hydrogen chloride in dioxane (4 M) was used in place of hydrogen chloride in EtOAc. ^1H NMR (500 MHz, CD_3OD): δ 8.75 (d, 1H), 8.19 (dd, 1H), 7.55 (d, 1H), 7.4-7.2 (m, 5H), 3.78 (m, 1H), 3.62 (dd, 1H), 3.48 (m, 1H), 3.43 (dd, 1H), 1.22 (d, 3H). LC-MS: m/e 261 $(M + H)^+$ (2.2 min).

REFERENCE EXAMPLE 19



N-[2-(3-Bromophenyl)-3-(5-chloro-2-pyridyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

Step A 3-Bromophenylacetone

To a solution of N-methoxy-N-methylacetamide (10 g, 100 mmol) in 100 mL anhydrous ether at 0°C was added 3-bromobenzylmagnesium bromide (0.25 M in

ether, 200 mL, 50 mmol). The reaction was allowed to warm to room temperature overnight and was quenched by the addition of saturated ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with hexane (100 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.45-7.40 (m, 2H), 7.26 (t, 1H), 7.19 (d, 1H), 2.20 (s, 3H).

Step B <u>3-(3-Bromophenyl)-4-(5-chloro-2-pyridyl)-2-butanone</u>

A suspension of 5-chloro-2-methylpyridine (Reference Example 18, Step A, 6.4 g, 50 mmol) and N-bromosuccinimide (12.5 g, 70 mmol) in 100 mL carbon tetrachloride was heated to gentle reflux (bath temperature 90°C), and 2,2'-azobisisobutyronitrile (0.74 g) was added in several portions over 30 min. After stirring at this temperature for 5 h, the reaction mixture was concentrated. The resulting slurry was diluted with EtOAc (100 mL) and was washed with water (100 mL), saturated aqueous sodium bicarbonate/saturated aqueous sodium thiosulfate, and brine. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 2 to 15% ether/CH_2Cl_2 (1:1) in hexane to afford 2-bromomethyl-5-chloropyridine (6.0 g, 60%), which was used immediately for the ensuing reaction. Thus, to a vigorously stirred solution of 2-bromomethyl-5-chloropyridine (6.0 g, 29 mmol) and 3-bromophenyl acetone (Step A, 6.0 g, 28 mmol) and tetrabutylammonium iodide (20 mg) in 30 mL CH_2Cl_2 at -78°C was added cesium hydroxide monohydrate (10 g, 60 mmol), and the reaction was allowed to slowly warm to room temperate overnight. The reaction mixture was partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 5 to 40% EtOAc in hexane to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.44 (d, 1H), 7.66 (dd, 1H), 7.46-7.41 (m, 2H), 7.24 (t, 1H), 7.22 (d, 1H), 7.15 (d, 1h), 4.42 (dd, 1H), 3.54 (dd, 1H), 3.07 (dd, 1H), 2.12 (s, 3H). LC-MS: m/e 338 $(M + H)^+$ (3.0 min).

Step C <u>3-(3-Bromophenyl)-4-(5-chloro-2-pyridyl)-2-butanol</u>

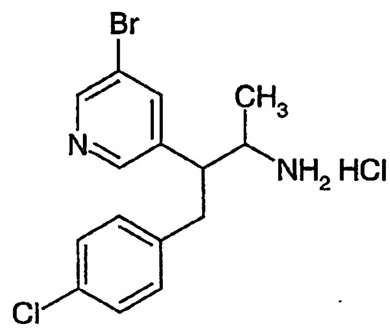
To a solution of 3-(3-bromophenyl)-4-(5-chloro-2-pyridyl)-2-butanone (Step B, 6.7 g, 20 mmol) in 50 mL anhydrous THF at -78°C was added lithium tri(sec-butyl)borohydride (1.0 M in THF, 30 mL, 30 mmol), and the reaction was allowed to warm to room temperature overnight. The reaction was cooled to 0°C, and was

carefully added 2 M hydrochloric acid (50 mL), and the resulting mixture was partitioned between hexane (200 mL) and water (200 mL). The aqueous layer was separated and the organic layer extracted with 2 M hydrochloric acid (2 x 100 mL). The combined aqueous extracts were neutralized with 5 N aqueous sodium hydroxide (pH > 12), and was extracted with EtOAc (2x200 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to afford the title compound.

Step D <u>*N*-[2-(3-Bromophenyl)-3-(5-chloro-2-pyridyl)-1-methylpropyl]amine, hydrochloride</u>

The product of Step C (5.9 g, 17 mmol) was converted to the title compound following the procedure described in Reference Example 18, Steps C-D. LC-MS: m/e 338 $(M + H)^+$ (2.3 min).

REFERENCE EXAMPLE 20



<u>*N*-[2-(5-Bromo-2-pyridyl)-3-(4-chlorophenyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)</u>

Step A <u>5-Bromo-3-pyridylacetone</u>

A mixture of 3,5-dibromopyridine (50 g, 0.21 mol), isopropenyl acetate (26 mL, 0.23 mmol), tris(dibenzylideneacetone)dipalladium (1.0 g, 1.1 mmol) and 2-(diphenylphosphino)-2'(N,N-dimethylamino)biphenyl (1.6 g, 4.2 mmol) in 400 mL toluene was heated at 100°C under nitrogen for 2 h. The reaction mixture was cooled to room temperature, and was concentrated to about 100 mL. The resulting mixture was loaded onto a silica gel column, which was eluted with 0 to 60% EtOAc in hexane to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.54 (br s, 1H), 8.33 (br s, 1H), 7.88 (br s, 1H), 3.90 (s, 2H), 2.25 (s, 3H).

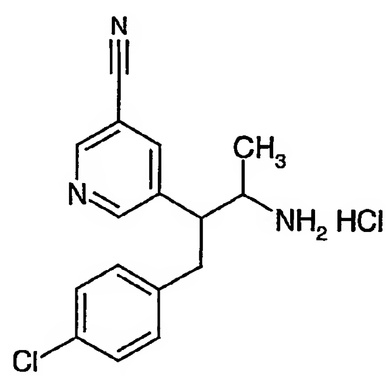
Step B 3-(5-Bromo-3-pyridyl)-4-(4-chlorophenyl)-2-butanol

The title compound was prepared following the procedure described in Reference Example 19, Step B-C, substituting 2-bromomethyl-5-chloropyridine with 4-chlorobenzyl chloride and 3-bromophenylaceatone with 5-bromo-3-pyridylacetone (Step A). ^{1}H NMR (500 MHz, CD3OD): δ 8.43 (d, 1H), 8.24 (d, 1H), 7.98 (dd, 1H), 7.17 (d, 2H), 7.07 (d, 2H), 4.04 (m, 1H), 3.16 (dd, 1H), 3.0-2.9 (m, 2H), 1.04 (d, 3H).

Step C *N*-[2-(5-Bromo-3-pyridyl)-3-(4-chlorophenyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

The title compound was prepared following the procedure described for Reference Example 4, Step B. LC-MS: m/e 339 $(M + H)^+$ (2.5 min).

REFERENCE EXAMPLE 21



N-[3-(4-Chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

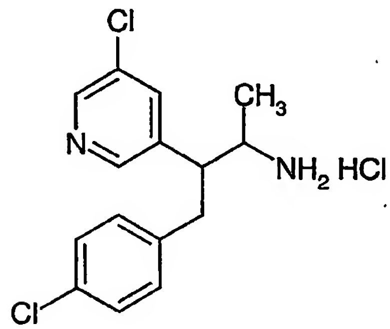
Step A 5-Cyano-3-pyridylacetone

The title compound was prepared following the procedure described for Reference Example 20 substituting 3,5-dibromopyridine with 5-bromonicotinonitrile (5-bromo-3-cyanopyridine) at Step A. ^{1}H NMR (400 MHz, CD3OD): δ 8.89 (d, 1H), 8.60 (d, 1H), 8.02 (t, 1H), 3.98 (s, 2H), 2.24 (s, 3H).

Step B *N*-[3-(4-Chlorophenyl)-2-(5-cyano-2-pyridyl)-1-methylpropyl]amine hydrochloride (Diastereomer α/β 5:1)

The title compound was prepared following the procedure described for Reference Example 5 substituting 3-pyridylacetone with 5-cyano-3-pyridylacetone (Step A). LC-MS: m/e 286 $(M + H)^+$ (1.9 min).

REFERENCE EXAMPLE 22



N-[3-(4-Chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

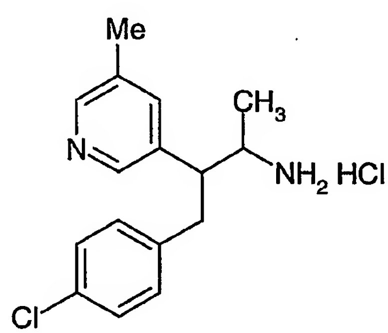
Step A 5-Chloro-3-pyridylacetone

The title compound was prepared following the procedure described for Reference Example 20 substituting 3,5-dibromopyridine with 3,5-dichloropyrdine and 2-(diphenylphosphino)-2'(N,N-dimethylamino)biphenyl with 2-(di-t-butylphosphino) biphenyl at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 8.42 (d, 1H), 8.27 (d, 1H), 7.73 (dd, 1H), 3.90 (s, 2H), 2.25 (s, 3H).

Step B N-[3-(4-Chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]amine hydrochloride (Diastereomer α)

The title compound was prepared following the procedure described for Reference Example 20, Step B-C substituting 5-bromo-3-pyridylacetone with 5-chloro-3-pyridylacetone at Step B. LC-MS: m/e 295 $(M + H)^+$ (1.9 min).

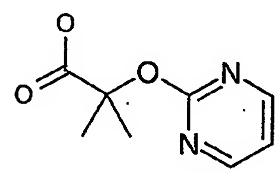
REFERENCE EXAMPLE 23



N-[3-(4-Chlorophenyl)-2-(5-methyl-3-pyridyl)-1-methylpropyl]amine hydrochloride(Diastereomer α)

The title compound was prepared following the procedure described for Reference Example 17 substituting 2-(*N-tert*-butoxycarbonyl)amino-3-(3-bromophenyl)-4-(4-chlorophenyl)butane with 2-(*N-tert*-butoxycarbonyl)amino-3-(5-bromo-3-pyridyl)-4-(4-chlorophenyl)butane (intermediate of Reference Example 20, Step B) at Step A. LC-MS: m/e 275 $(M + H)^+$ (1.3 min).

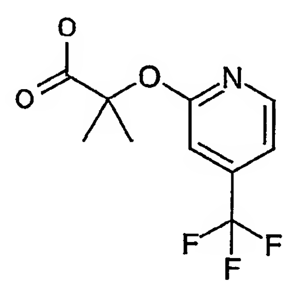
REFERENCE EXAMPLE 24



2-Methyl-2-(2-pyrimidyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 13 substituting 5-chloro-2-hydroxpyridine with 2-hydroxpyrimidine at Step A. ^1H NMR (500 MHz, CD_3OD): δ 8.53 (d, 2H), 7.09 (t, 1H), 1.74 (s, 6H).

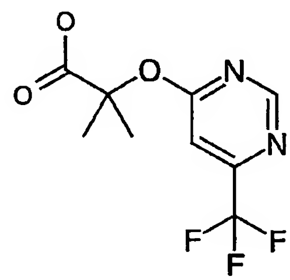
REFERENCE EXAMPLE 25



2-Methyl-2-(4-trifluoromethyl-2-pyridyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 13 substituting 5-chloro-2-hydroxpyridine with 4-trifluoromethyl-2-hydroxpyridine at Step A. ^1H NMR (500 MHz, CD_3OD): δ 8.30 (d, 1H), 7.18 (d, 1H), 7.05 (s, 1H), 1.71 (s, 6H).

REFERENCE EXAMPLE 26



2-Methyl-2-(6-trifluoromethyl-4-pyrimidyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 13 substituting 5-chloro-2-hydroxpyridine with 6-trifluoromethyl-4-hydroxpyrimidine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 8.81 (s, 1H), 7.28 (s, 1H), 1.75 (s, 6H). LC-MS: m/e 251 $(M + H)^+$ (2.1 min).

REFERENCE EXAMPLE 27

2-Methyl-2-(5-trifluoromethyl-2-pyridyloxy)propionic Acid

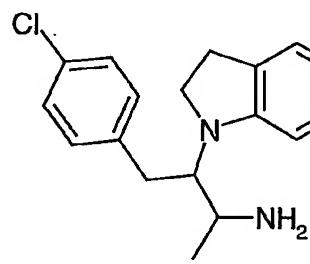
Two nitrogen flushed, 12 L 3-necked round bottom flasks, each fitted with a thermometer and a reflux condenser were charged with KHMDS in THF (0.91 M, 3.52 L each, 3.205 mol, 1.5 eq). The solutions were cooled to –70°C and stirred magnetically. Ethyl-2-hydroxyisobutyrate (98%) (463 mL, 447g, 3.38 mol) was added to each flask over 30 min, keeping the reaction temperature below –62°C. After 10 min 2-chloro-5-trifluormethylpyridine (388 g, 2.14 mol) was added to each flask in one portion. The cooling bath was removed and the reactions were allowed to warm to 20°C overnight (ca 16 hr.).The reactions were monitored by TLC (silica, 90/10 Hex/EtOAc) and HPLC:

Sodium hydroxide (1.36 L, 5N) was added to each reaction flask and the reactions were refluxed overnight (ca 22 hr). The reactions were concentrated together on a rotary evaporator to remove the THF. To the concentrate was added water (4L) and the solution extracted with n-heptane (2 x 4L). The aqueous layer was added over 10 min to 2N HCl (9L, 18 mol) with stirring. The resulting suspension was aged for 30 min (temperature 30°C) then filtered. The cake was washed with water (3 x 2L), and air-dried to a damp tan solid.

The material was dissolved in n-heptane (4 L) at 65°C. IPAc (1 L) and DARCO KB (40 g, 100 mesh) were added. The mixture was stirrer for 15 min,

filtered through CELITE diatomaceous earth, and the cake washed with 4:1 heptane/IPAc (3 x 500 mL). The filtrate was concentrated to ca. 2 L affording a white suspension. The slurry was flushed with heptane (2 x 3L) and concentrated to ca. 3L. The resulting white suspension was cooled to 0°C and aged 1 hr. The product was filtered and the cake washed with cold heptane (1 L) to provide the title compound as white crystalline material. HPLC Column: YMC Combiscreen Pro C18, 50 x 4.6mm; Mobile phase: A 0.1%TFA in H_2O; B CH_3CN. Gradient: 90/10 A/B to 10/90 A/B in 4 min. Flow rate: 4 mL/min. Detection: 254 nm. RT 2-chloro-5-trifluormethylpyridine 2.1 min. RT 2-ethoxy-5-trifluoromethylpyridine 2.9 min. RT Product Ester 3.1 min. RT Final Acid 2.05 min.

REFERENCE EXAMPLE 28



2-Amino-3-indolin-N-yl-4(4-chloro)phenylbutane

Step A. Ethyl 3-(4-chlorophenyl)-2-indolin-N-ylpropanoate. In an oven-dried flask under an atmosphere of nitrogen, 1.1g $LiOH{\cdot}H_2O$ (26.25 mmol) in DMF (20 mL) was added to a stirring suspension of 4 angstrom molecular sieves. After 30 minutes of stirring at room temperature 2.8 mL (25mmol) indoline was added dropwise. After one hour at room temperature 2.9 mL (26.25 mmol) ethyl bromoacetate was added dropwise. After 1.5 h the solid material was filtered and the residue was washed with copious amounts of EtOAc. The organics were washed 3 times with water and the organic material was dried over $MgSO_4$. The solvents were evaporated under reduced pressure. The crude material was then dissolved in 75 mL anhydrous THF, charged into an oven dried round bottom flask under an atmosphere of nitrogen, cooled to –78°C, and then treated with 26.25 mL of a 1M solution of NaHMDS. The solution was allowed to stir for 30 minutes at –78°C after which the enolate was alkylated with 5.4 g (26.25 mmol) of parachlorobenzyl bromide (solution

in 25 mL anhydrous THF). The reaction was allowed to warm to room temperature overnight. The next day the reaction was quenched with water. The aqueous layer was extracted with 3 large portions of EtOAc. The combined organics were dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified by flash chromatography which yielded the title compound as a yellow oil. LC/MS m/e=331 (M+1). TLC R_f=0.22 (20:1 hexanes : EtOAc). ^{1}H NMR (500 MHz , $CDCl_3$): δ 1.11 (t, J=3.55 Hz, 3H), 2.96 (m, 2H), 3.06 (m, 1H), 3.25 (m, 1H), 3.60 (t, 2H), 4.07 (m, 2H), 4.36 (t, J=3.75 Hz, 1H).

Step B. N,O-dimethyl-3-(4-chlorophenyl)-2-indolin-N-ylpropanamide. In an oven-dried flask under an atmosphere of nitrogen, 11.75 mL of a 1-M solution of $(CH_3)_2AlCl$ in CH_2Cl_2 was added via addition funnel to a stirring suspension of 1.15 g (11.75 mmol) N,O-dimethylhydroxylamine hydrochloride at 0°C. After warming to room temperature a solution of 970 mg (2.94 mmol) of ethyl 3-(4-chlorophenyl)-2-indolinylpropanoate (obtained from Step A) in 10 mL was added via addition funnel. After stirring at room temperature for 5 h, 35 mL of a pH 8 phospate buffer solution was added and the resulting mixture was stirred vigorously for 30 minutes. The phases were separated and the aqueous layer was extracted 2 times with chloroform. The combined organics were washed with water and then dried over $MgSO_4$. A brown oil was collected. The crude material was carried on to the next step. TLC R_f=0.12 (10:1 hexanes : EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.83 (m, 1H), 2.97(m, 2H), 3.13 (s, 3H), 3.34 (m, 1H), 3.45 (s, 3H), 3.61 (m, 2H), 4.87 (b, 1H), 6.54 (d, 1H), 6.66 (t, J=7.1 Hz, 1H), 7.07 (t, J=7.1 Hz, 2H), 7.18 (d, J=8.5 Hz, 2H), 7.24 (d, J=8.5 Hz, 2H)

Step C. 4-(4-chlorophenyl)-3-indolin-N-ylbutan-2-one.

In an oven dried flask under an atmosphere of nitrogen, 2.8 mL if a 1-M solution of CH_3MgBr in THF was added dropwise to a stirring solution of N,O-dimethyl-3-(4-chlorophenyl)-2-indolinylpropanamide (from Step B, 965 mg) in 25 mL anhydrous THF. The solution was stirred for 4 h while being allowed to warm to room temperature. Then approximately 20 mL water were added. The mixture was extract three times with 50 mL ether. The combined extracts were dried over $MgSO_4$. The solvents were removed under reduced pressure yielding a brown oil which was carried on to the next step without purification. LC/MS m/e=301 (M+1). TLC R_f=0.5 (4:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.14 (s, 3H), 2.81 (dd, J=14.6, 6.6 Hz, 1H), 2.97 (t, J=8.5 Hz, 2H), 3.26 (m, 2H), 3.5 (m, 1H), 4.21 (dd, J=6.6, 6.6 Hz),

6.39 (d, J=8 Hz, 1H), 6.66 (dd, J=7, 7 Hz, 1H), 7.07 (m, 2H), 7.13 (d, J=8.5 Hz), 7.22 (d, J=8.3 Hz).

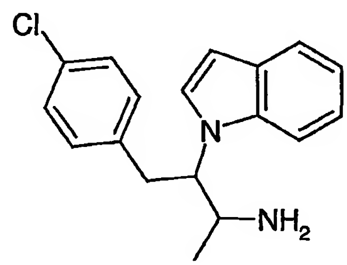
Step D. <u>4-(4-chlorophenyl)-3-indolin-N-ylbutan-2-one methoxime</u>.

A solution of 472 mg (1.573 mmol) of the product of Step C and 263 mg (3.147 mmol) of methoxylamine hydrochloride in anhydrous ethanol was treated with 255 μL (3.147 mmol) of pyridine. The solution was stirred for 2 h at room temperature. Solvent was removed under reduced pressure and the residue was partitioned between water and ether. The water was extracted with ether again. The extracts were then combined and dried over $MgSO_4$, filtered and concentrate to obtain crude material. Both the E and Z isomers were carried onto the next step. LC/MS m/e=330 (M+1). TLC R_f=.77 and .65 (4:1 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78 (2s, 1H), 2.88 (dd, J=6.2, 13.8 Hz, 1H), 2.95 (m, 2H), 3.30 (m, 2H), 3.45 (m, 1H), 3.75 and 3.89 (2s, 3H), 4.21 (dd, J=6.9, 7.8 Hz, 1H), 6.28 and 6.47 (2d, J=8.1, 1H), 6.61 (m, 1H), 7.02 (m, 2H), 7.22 (m, 4H).

Step E. <u>2-Amino-3-indolin-N-yl-4(4-chloro)phenylbutane</u>

In an oven-dried flask equipped with a water condenser under an atmosphere of nitrogen, a solution of 301 mg (0.914 mmol) 4-(4-chlorophenyl)-3-indolinylbutan-2-one methoxime (obtained from Step D) in 1.5 mL anhydrous THF was treated with 3.7 mL (3.7 mmol) of 1M BH_3·THF at room temperature. The solution was then heated to 75°C for 2 days. The solution was then cooled to 0°C and treated with chips of ice until bubbling subsided. 500 μL of 20% KOH were then added and the solution was heated at 45°C for 2h. The solution was then cooled to room temperature and extracted with ether 3x. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to afford crude amine which was used in the next experiment without further purification. LC/MS m/e=302 (M+1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13, 1.14 (2d, J=6.5 Hz, 1H), 1.55-1.60 (m, 2H), 2.80-3.10 (m, 4H), 3.30-3.60 (m, 2H), 6.348 and 6.38 (2d, J=7.9 Hz, 1H), 6.50-6.78 (m, 2H), 6.95-7.24 (m, 5H)

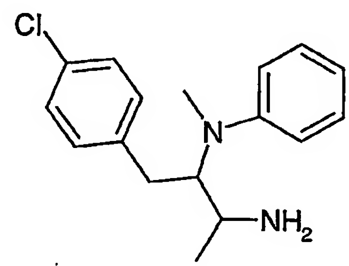
REFERENCE EXAMPLE 29



2-Amino-3-indol-N-yl-4(4-chloro)phenylbutane

This compound was prepared in an analogous manner to Reference Example 28 except that during Step A, sodium hydride was used as the base instead of the lithium hydroxide monohydrate/molecular sieves combination. LC/MS: calculated for $C_{18}H_{19}ClN_2$ 299, observed m/e 300 $(M + H)^+$ (2.4 min).

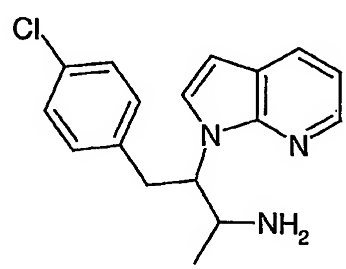
REFERENCE EXAMPLE 30



2-Amino-3-(N-methyl, N-phenyl)amino-4(4-chloro)phenylbutane

This compound was prepared in an analogous manner to Reference Example 28. LC/MS: calculated for $C_{17}H_{21}ClN_2$ 289, observed m/e 290 $(M + H)^+$ (2.4 min).

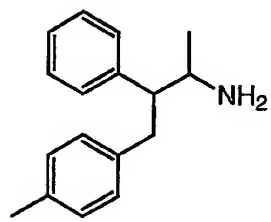
REFERENCE EXAMPLE 31



2-Amino-3-(7-azaindol-N-yl)-4(4-chloro)phenylbutane

This compound was prepared in an analogous manner to Reference Example 28. LC/MS: calculated for $C_{17}H_{18}ClN_3$ 300, observed m/e 301 $(M + H)^+$ (2.7 min).

REFERENCE EXAMPLE 32



4-(4-Methylphenyl)-3-phenylbutan-2-amine (mixture of 4 isomers)

Step A 1-Phenylacetone

To a solution of N-methyl-N-methoxyacetamide (9.9mL. 97 mmol) in ether (300 mL) at 0°C was added benzylmagnesium chloride (97 mL a 1M solution in ether). The cloudy, white reaction mixture was warmed to room temperature for 2 h and then quenched by careful addition of 1N hydrochloric acid (100 mL). The organic phase was separated, washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography on silica gel eluting from 0-10% EtOAc/hexane to give the title compound. ^1H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, J = 7.1Hz, 2H), 7.30 (t, J = 7.3Hz, 1H), 7.24 (d, J = 7.3Hz, 2H), 3.72 (s, 2H), 2.18 (s, 3H). LC-MS: m/e 135 $(M + H)^+$ (1.95 min).

Step B 4-(4-Methylphenyl)-3-phenylbutan-2-one

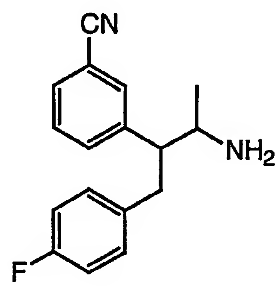
1-Phenylacetone (200 mg, 1.49 mmol) was mixed with powdered potassium hydroxide (167 mg, 2.98 mmol) and tetra-n-butylammonium bromide (1mol %, 5 mg) in a flask without solvent. This mixture was stirred at room temperature for 90 min. before the addition of 1-(chloromethyl)-4-methylbenzene (198 μl, 1.49 mmol). The reaction mixture was then stirred overnight before diluting with water and CH_2Cl_2. The aqueous layer was separated and neutralized to pH 7 with 2N hydrochloric acid and extracted again into CH_2Cl_2. The combined organic washes were dried with $MgSO_4$ and concentrated. The crude material was purified by column chromatography on silica gel eluting from 0-10% EtOAc/hexane to give the title compound. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, J = 7.0 Hz, 2H), 7.29 (t, J = 7.4

Hz, 1H), 7.23 (d, J = 7.1 Hz, 2H), 7.05 (d, 7.8 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 3.94 (t, J = 7.3 Hz, 1H), 3.43 (dd, J = 13.9, 7.5 Hz, 1H), 2.91 (dd, J = 14, 7.1 Hz, 1H), 2.32 (s, 3H), 2.08 (s, 3H). LC-MS: m/e 239 $(M + H)^+$ (3.61 min).

Step C 4-(4-Methylphenyl)-3-phenylbutan-2-amine

To a solution of the 4-(4-methylphenyl)-3-phenylbutan-2-one (308 mg, 1.29 mmol) in 7M ammonia in MeOH (5 mL) and acetic acid (3 mL) was added sodium cyanoborohydride (130 mg, 2.06 mmol) and the reaction stirred at room temperature overnight. The reaction was quenched by pouring into 2M sodium carbonate solution and extracted into EtOAc. The aqueous layer was salted and re-extracted. The combined organic extracts were dried over $MgSO_4$ and concentrated to give the title compound as a mixture of 4 isomers which was used without further purification. LC-MS: m/e 240 $(M + H)^+$ (2.22 min).

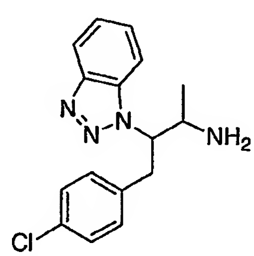
REFERENCE EXAMPLE 33



3-[2-Amino-1-(4-fluorobenzyl)propyl]benzonitrile

Prepared using the procedures described in Example 5, Steps B and C using 3-(2-oxopropyl)benzonitrile and 1-(chloromethyl)-4-fluorobenzene as the reactants in Step B. LC-MS: m/e 269 $(M + H)^+$ (2.87 min).

REFERENCE EXAMPLE 34



2-(1H-1,2,3-Benzotriazol-1-yl)-3-(4-chlorophenyl)-1-methylpropylamine

Step A 2-(1H-1,2,3-Benzotriazol-1-yl)-N-methoxy-N-methylacetamide

A mixture of 1.77 g (10 mmol) of 2-(1H-1,2,3-benzotriazol-1-yl)acetic acid, 1.07 g (11 mmoles) of N,O-dimethylhydroxylamine hydrochloride, 5.8 g (11 mmol) of PyBOP, and 3.4 mL (24.2 mmol) of diisopropylethylamine in 50 mL CH_2Cl_2 was stirred overnight at RT. This mixture was partitioned between EtOAc and water. The organic layer was washed with brine and dried over anhydrous MgSO4. Solvent removal afforded a crude product which was purified on silica gel using 60% EtOAC in hexane as solvent to give 2.01 g the desired amide as a solid. ^{1}H NMR: ($CDCl_3$): δ 3.26 (s, 3H), 3.84 (s, 3H), 5.63 (s, 2H), 7.35-8.2 (m, 4H).

Step B 2-(1H-1,2,3-Benzotriazol-1-yl)-3-(4-chlorophenyl)-N-methoxy-N-methyl-propanamide.

To a solution of 2.0 g (9 mmol) of 2-(1H-1,2,3-benzotriazol-1-yl)-N-methoxy-N-methylacetamide in 15 mL anhydrous THF at –78 °C, 10 mL (10 mmol) of 1M lithium bis(trimethylsilyl)amide was added dropwise. After stirring for 25 min, a solution of 2.06 g (10 mmol) of 4-chlorobenzyl bromide in 2 mL anhydrous THF was added. The resulting reaction mixture was allowed to warm to RT and stirred for 6 h. This reaction was quenched, diluted with 75 mL EtOAc and washed 3 times with 10 mL each of brine, After drying the organic phase solvent removal afforded a crude product which was purified on silica gel using 40% EtOAc in hexane as solvent to afford the desired product as a solid. ^{1}H NMR: ($CDCl_3$): δ 3.2 (s, 3H), 3.34 (s, 3H), 3.52 (m, 1H), 3.7 (m, 1H), 6.32 (t, 1H), 6.9-8.2 (m, 8H).

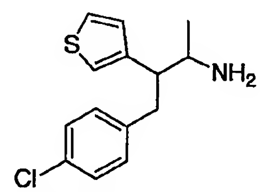
Step C 2-(1H-1,2,3-Benzotriazol-1-yl)-3-(4-chlorophenyl)-butan-2-one.

To a solution of 1.73 g (5 mmol) of 2-(1H-1,2,3-benzotriazol-1-yl)-3-(4-chlorophenyl)-N-methoxy-N-methyl-propanamide in 10 mL anhydrous THF at 0 °C, 4 mL (10 mmol) of 2.5M methyl magnesium bromide in ether was added. The reaction mixture was stirred for 4 h as it warmed to RT. The reaction was quenched by adding 10 mL 1N HCl and the resulting mixture was partitioned between EtOAc and water. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. Solvent removal gave a crude ketone, which was purified on silica gel using 40% EtOAc in hexane to provide the desired ketone.

Step D 2-(1H-1,2,3-Benzotriazol-1-yl)-3-(4-chlorophenyl)-1-methyl propylamine

To a solution of 1.18 g (4 mmol) of 2-(1H-1,2,3-benzotriazol-1-yl)-3-(4-chlorophenyl)-butan-2-one in 8.5 mL (60 mmol) of 7N ammonia in MeOH at 0 °C, 4 mL (964 mmol) of glacial acetic acid was added followed by 410 mg (6.5 mmol) of sodium cyanoborohydride. The reaction mixture was allowed to warm to RT and stirred overnight. The reaction was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified on silica gel using a mixture of 5% 2N methanolic ammonia solution and 95% CH_2Cl_2 to give the desired amine as a mixture of diastereomers. LC-MS, RT = 2.0 min, m/e = 301.

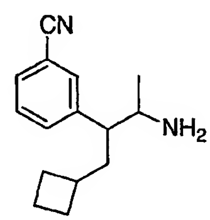
REFERENCE EXAMPLE 35



3-(4-Chlorophenyl)-2-(thiophene-3-yl)-1-methylpropylamine

The title amine was prepared by the method described in Reference Example 34, substituting thiophene-3-acetic acid for 2-(1H-1,2,3-benzotriazol-1-yl)acetic acid in Step A. LC-MS, RT = 2.19 min, m/e = 266.

REFERENCE EXAMPLE 36



2-(3-Cyanophenyl)-3-cyclobutyl-1-methylpropylamine

Step A 1-(3-Cyanophenyl)acetone

The title compound was prepared from 3-bromobenzonitrile and isopropenyl acetate by the procedure of Reference Example 20, Step A.

Step B 3-(3-Cyanophenyl)-4-cyclobutyl-butan-2-one

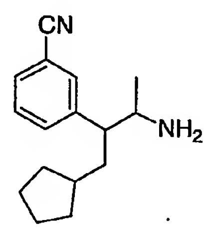
To a solution of 1.45 g (9.07 mmol) of 1-(3-cyanophenyl)acetone in 18 mL acetonitrile, 1.1 mL (9.5 mmol) cyclobutyl bromide and 5.91 g (18.1 mmol) cesium carbonate were added. After heating the solution in a 60 °C bath overnight, it was cooled and filtered. The filtrate was partitioned between water and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated. The residue was purified on a flash column using a gradient of 5-10% EtOAc/hexane to isolate the title compound. ^{1}H NMR: (500 MHz, $CDCl_3$): δ 1.5-2.2 (m, 9H), 2.13 (s, 3H), 3.64 (m, 1H), 7.4-7.7 (m, 4H).

Step C 2-(3-Cyanophenyl)-3-cyclobutyl-1-methylpropylamine

This amine was prepared by following the method of Reference Example 3, Steps E-I. LC-MS, RT = 2.48 min, m/e = 229.

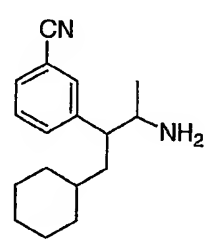
The compounds of Reference Examples 37 and 38 were obtained by procedures described in Reference Example 36.

REFERENCE EXAMPLE 37



2-(3-Cyanophenyl)-3-cyclopentyl-1-methylpropylamine
LC-MS, RT = 2.7 min, m/e = 243.

REFERENCE EXAMPLE 38



2-(3-Cyanophenyl)-3-cyclohexyl-1-methylpropylamine
LC-MS, RT = 2.8 min, m/e = 257.

EXAMPLE 1

Automated Synthesis of a One Dimensional Amide Library

The following synthesis of a 1-dimensional, single, pure compound library was performed on a MYRIAD CORE System. All reaction vessels were dried under a stream of nitrogen at 120°C for 12 h prior to use. All solvents were dried over sieves for at least 12 h prior to use. An appropriate stock solution of *N*-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-amine hydrochloride (alpha isomer) was prepared immediately prior to use in pyridine with 0.05 equivalents (relative to *N*-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-amine hydrochloride (alpha isomer)) of dimethylaminopyridine added; the diverse carboxylic acids available from commercial sources were dissolved immediately prior to use in DMSO. The relative amounts of reactants and coupling reagents are listed in Table 1.

Table 1.

Substance	Amount per reaction vessel	MW	Concentration	mmols	Equivs.
Acid in DMSO	1 mL	N/A	0.2 M	0.2	1.67
EDC/HOBt Cocktail in Deuterated Chloroform	0.8 mL	EDC: 191.71 HOBt: 135.13	0.25 M each	0.2 each	1.67 each
Amine in Pyridine with catalytic dimethylaminopyridine (~0.05 eq.)	0.6 mL	294.227	0.2M	0.12	1.0

Procedure: To vessel one of a total of 192 dry, 10 mL fritted MYRIAD reaction vessels under nitrogen was added the appropriate diverse acid subunit (1.0 mL, 0.2 mmoles, 0.2 M in DMSO); this was repeated for the remaining 191 reactions until the diversity acids had been enumerated to all 192 reaction vessels. To each of 192 reaction vessels under nitrogen was then added the EDC/HOBt cocktail (0.8 mL, 0.2 mmoles, 0.25 M each in deuterated chloroform). Finally, to each of the 192 reaction

vessels was added *N*-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-amine hydrochloride (alpha isomer) (0.6 mL, 0.12 mmoles, 0.2M in pyridine). The reactions were then aged for 4 h at room temperature (20-25° C) followed by 16 h at 65°C with nitrogen sparging agitation (1s pulse of nitrogen every 30 minutes). The crude reactions were analyzed by HPLC-MS Method 1.

Analytical LC Method 1:

Column:	MetaChem Polaris C-18A, 30 mm X 4.6 mm, 5.0 µm
Eluent A:	0.1% TFA in Water
Eluent B:	0.1 % TFA in Acetonitrile
Gradient:	5% B to 95 % B in 3.3 minutes, ramp back to 5% B in 0.3 min
Flow:	2.5 mL/min.
Column Temp.:	50° C
Injection amount:	5 uL of undiluted crude reaction mixture.
Detection:	UV at 220 and 254 nm.

MS: API-ES ionization mode, mass scan range (100-700)

ELSD: Light Scattering Detector

Crude reactions were purified by preparative HPLC using UV based detection (Preparative method 2). The collected fractions were then analyzed for purity by LC-MS (Analytical method 3); fractions found to be greater than 90% purity were pooled into tared 40 mL EPA vials and lyophilized.

Preparative LC Method 2:

Column:	MetaChem Polaris C-18A, 100 mm X 21.2 mm, 10 µm
Eluent A:	0.1% TFA in Water
Eluent B:	0.1% TFA in Acetonitrile
Pre-inject Equilibration:	1.0 min
Post-Inject Hold:	0.0 min
Gradient:	10% B to 100 % B in 6.0 minutes, hold at 100% B for an additional 2.0 minutes, ramp back from 100% B to 10% B in 1.5 minutes.
Flow: 25 mL/min.	
Column Temp.:	ambient

Injection amount: 1.5 mL undiluted crude reaction mixture.
Detection: UV at 220 and 254 nm.

Analytical LC Method 3:

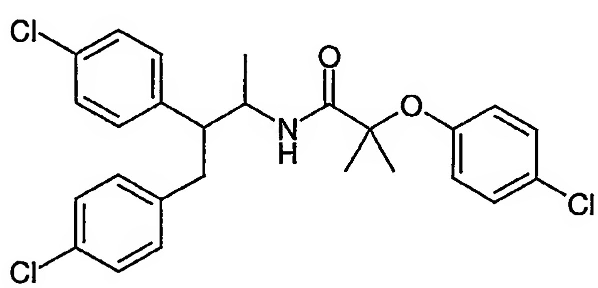
Column: MetaChem Polaris C-18A, 30 mm X 2.0 mm, 3.0 µm
Eluent A: 0.1% TFA in Water
Eluent B: 0.1% TFA in Acetonitrile
Gradient: 5% B to 95 % B in 2.0 minutes, ramp back to 5% B in 0.1 min
Flow: 1.75 mL/min.
Column Temp.: 60°C
Injection amount: 5 uL of undiluted fraction.
Detection: UV at 220 and 254 nm.
MS: API-ES ionization mode, mass scan range (100-700)
ELSD: Light Scattering Detector

Lyophilization Parameters

Initial Freeze Setpoint: 1 h at –70°C
Drying Phase Condenser Setpoint: -50°C
Drying Phase Table:

Shelf Temperature (C)	Duration (minutes)	Vacuum Setpoint (mTorr)
-60°	240	25
-40°	240	25
5°	480	25
20°	1000	25

EXAMPLES 2 and 3



N-[2,3-Bis(4-Chlorophenyl)-1-methylpropyl]-2-(4-chlorophenyloxy)-2-methylpropanamide (Diastereomers α and β).

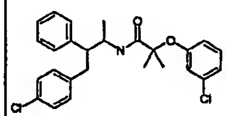
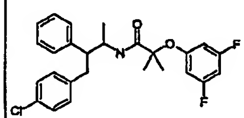
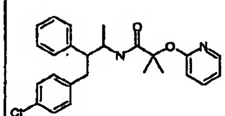
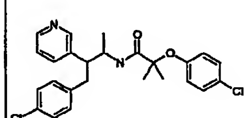
To a solution of 2-(4-chlorophenyloxy)-2-methylpropionic acid (Aldrich, 0.22 g, 1.0 mmol) in CH_2Cl_2 (2 mL) at 0°C was added a drop of DMF and oxalyl chloride (0.27 mL, 3.0 mmol). After stirring at room temperature for 1 h, the reaction mixture was concentrated on a rotary evaporator and dried under vacuum, and the resulting crude acyl chloride was used without further purification. Thus, the crude acyl chloride was dissolved in 1 mL CH_2Cl_2 and was added to a suspension of 2-amino-3,4-bis(4-chlorophenyl)butane hydrochloride salt (Reference Example 1) (diastereomer α contaminated with some diastereomer β, 0.20 g, 0.60 mmol) and *N*-methylmorpholine (0.27 mL, 2.4 mmol) in 4 mL CH_2Cl_2. After stirring at room temperature for 6 h, the reaction mixture was loaded onto a silica gel column, which was eluted with 10% EtOAc to give a pure faster eluting isomer (diastereomer α) and a slower eluting isomer (diastereomer β).

Diastereomer α: ^{1}H NMR (500 MHz, CD_3OD): δ 7.24 (d, 2H), 7.20 (d, 2H), 7.05 (d, 2H), 7.01 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 4.25 (m, 1H), 3.03 (dd, 1H), 2.88 (ddd, 1H), 2.67 (dd, 1H), 1.59 (s, 3H), 1.53 (s, 3H), 0.88 (d, 3H). LC-MS: m/e 490$(M + H)^+$ (4.7 min).

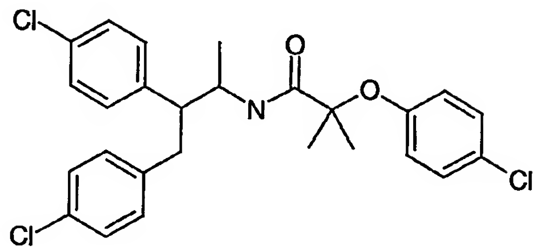
Diastereomer β: ^{1}H NMR (500 MHz, CD_3OD): δ 7.16 (d, 2H), 7.14 (d, 2H), 7.09 (d, 2H), 6.99 (d, 2H), 6.88 (d, 2H), 6.64 (d, 2H), 4.33 (m, 1H), 3.12 (dd, 1H), 3.03 (ddd, 1H), 2.74 (dd, 1H), 1.36 (s, 3H), 1.30 (d, 3H), 1.30 (s, 3H). LC-MS: m/e 490$(M + H)^+$ (4.7 min).

Examples 4-7 (Table 2) were prepared following the procedures described in Examples 2 and 3 substituting 2-amino-3,4-bis(4-chlorophenyl)butane hydrochloride salt with the appropriate amines from the Reference Examples and 2-(4-chlorophenyloxy)-2-methylpropionic acid with the appropriate acids from the Reference Examples. In some cases, commercial acids or acyl chlorides were employed, and *N*-diisopropyl-ethylamine may be used in place of *N*-methylmorpholine with similar results. The diastereomer designations (α or β) correspond to designations of the starting amines.

Table 2. Compounds prepared according to the methods described in Examples 2-3.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*	Diaster-eomer α and/ or β
4.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3-chlorophenyloxy)-2-methylpropanamide		4.5	456	α
5.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3,5-difluorophenyloxy)-2-methylpropanamide		4.4	458	α
6.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(2-pyridyloxy)-2-methylpropanamide		3.9	423	α
7.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-(3-pyridyl)propyl]-2-(4-chlorophenyloxy)-2-methylpropanamide		3.0	457	α

EXAMPLES 8 and 9



N-[2,3-Bis(4-Chlorophenyl)-1-methylpropyl]-2-(4-chlorophenyloxy)-2-methylpropanamide (Diastereomer α, Enantiomers A and B).

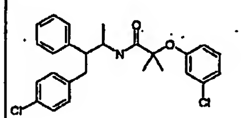
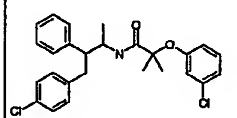
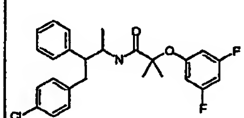
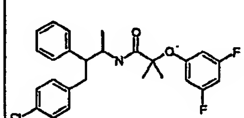
Preparative HPLC was performed on a Gilson HPLC system for the separation of enantiomers. Thus, a solution of *N*-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-2-(4-chlorophenyloxy)-2-methylpropanamide (Diastereomer α) (Example 60, 1.0 g) in hexane (3 mL)/ethanol (7 mL) was loaded onto a Chiralpak AD column (2 cm x 25 cm), which was eluted with 5% ethanol in hexane (flow rate 9 mL/min, 500 μL per injection) to give the two pure enantiomers.

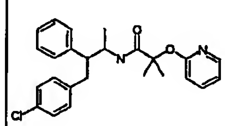
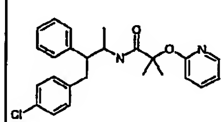
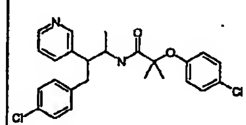
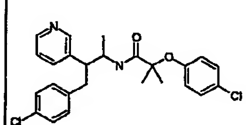
Faster eluting enantiomer (Enantiomer A): Analytical HPLC: retention time = 7.8 min (Chiralpak AD column, flow rate = 0.75 mL/min, 5% ethanol/hexane). LC-MS: m/e 490 $(M + H)^+$ (4.7 min).

Slower eluting enantiomer (Enantiomer B): Analytical HPLC: retention time = 9.6 min (Chiralpak AD column, flow rate = 0.75 mL/min, 5% ethanol/hexane). LC-MS: m/e 490 $(M + H)^+$ (4.7 min).

Examples 10-17 (Table 3) were isolated as single enantiomers following the procedures described in Examples 8-9 from the corresponding racemic material (Table 2) with appropriate modifications of (1) the eluent composition (4-15% ethanol/hexane), (2) flow rate (6-9 mL/min) and (3) injection volume (200 to 2000 μL).

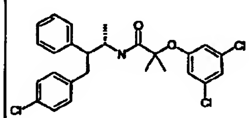
Table 3. Enantiomeric compounds isolated according to the methods described in Examples 8-9.

Ex. No.	Name	Structure	Retention time (min)	HPLC-mass spectrum *m/e*	Enan-tiomer A or B
10.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3-chlorophenyloxy)-2-methylpropanamide		4.5	456	A
11.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3-chlorophenyloxy)-2-methylpropanamide		4.5	456	B
12.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3,5-difluorophenyloxy)-2-methylpropanamide		4.3	458	A
13.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3,5-difluorophenyloxy)-2-methylpropanamide		4.3	458	B

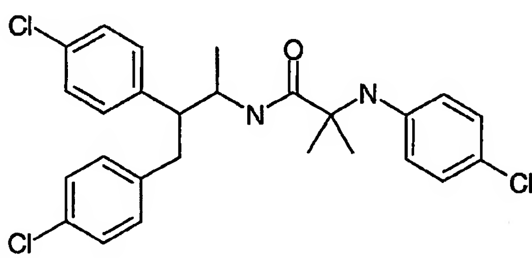
14.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(2-pyridyloxy)-2-methylpropanamide		3.9	423	A
15.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(2-pyridyloxy)-2-methylpropanamide		3.9	423	B
16.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-(3-pyridyl)propyl]-2-(4-chlorophenyloxy)-2-methylpropanamide		3.0	457	A
17.	*N*-[3-(4-Chlorophenyl)-1-methyl-2-(3-pyridyl)propyl]-2-(4-chlorophenyloxy)-2-methylpropanamide		3.0	457	B

Example 18 (Table 4) was prepared following the procedures described in Examples 2-3 employing *N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-amine, hydrochloride from Reference Example 4 coupled to the appropriate carboxylic acid.

Table 4. Single enantiomeric compounds prepared with *N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-amine, hydrochloride from Reference Example 4.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*
18.	*N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-2-(3,5-dichlorophenyloxy)-2-methylpropanamide		4.7	490

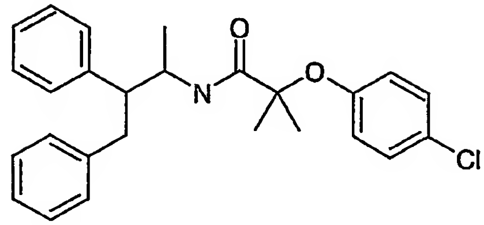
EXAMPLE 19



N-[2,3-Bis(4-chlorophenyl)-1-methylpropyl]-2-(4-chlorophenylamino)-2-methylpropanamide.

To a mixture of 2-amino-3,4-bis(4-chlorophenyl)butane hydrochloride salt (Diastereomer α, Section I, Reference Example 1, 0.31 g, 0.94 mmol) and 2-(4-chlorophenylamino)-2-methylpropionic acid (0.20 g, 0.94 mmol) in 5 mL CH_2Cl_2 was added *N*-methylmorpholine (0.41 mL, 3.5 mmol) and tris(pyrrolindinyl)phosphonium hexafluorophosphate (0.73 g, 1.4 mmol). After stirring at room temperature overnight, the reaction mixture was loaded onto a silica gel column eluted with 30% EtOAc in hexane to give the title compound. ^{1}H NMR (400 MHz, CD_3OD): δ 7.18 (d, 2H), 7.04 (d, 2H), 7.02 (d, 2H), 6.97 (d, 2H), 6.70 (d, 2H), 6.56 (d, 2H), 4.20 (m, 1H), 3.02 (dd, 1H), 2.78 (ddd, 1H), 2.64 (dd, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 0.82 (d, 3H). LC-MS: m/e 489 $(M + H)^+$ (4.3 min).

EXAMPLE 20

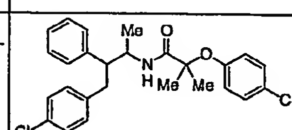


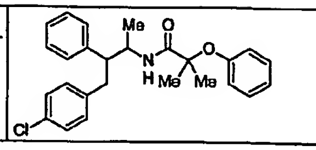
N-(2,3-Diphenyl-1-methylpropyl)-2-(4-chlorophenoxy)-2-methylpropanamide (Diastereomer β)

A solution of 2-(4-chlorophenoxy)-2-methylpropionic acid (20 mg, 0.095 mmol) in CH_2Cl_2 (1 mL) and DMF (10 μL) was treated with oxalyl chloride (11 μL). After 30 min the reaction was concentrated and the residue was dissolved in 1 mL CH_2Cl_2. This solution was added to a mixture of 16 mg N-(2,3-diphenyl-1-methylpropylamine (β isomer from Reference Example 2) and 1 mL saturated $NaHCO_3$. The reaction was stirred overnight and the organic layer was removed with a pipet. Purification of this solution by preparative TLC eluted with 30% EtOAc/hexane afforded the title compound. ^{1}H NMR: (500 MHz, $CDCl_3$): δ 1.17 (d, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 2.85-3.05 (m, 3H), 4.44(m, 1H), 6.37 (d, 1H), 6.75-7.4 (m, 14H). LC-MS: R_t = 4.4 min. m/e = 422.2 (M+1).

The following compounds in Table 5 were prepared following the procedures of Example 20 substituting an appropriate amine for N-(2,3-diphenyl-1-methylpropylamine and appropriate carboxylic acid for 2-(4-chlorophenoxy)-2-methyl-propionic acid.

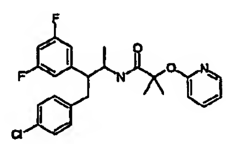
Table 5.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*
21.	*N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(4-chlorophenyloxy)-2-methylpropanamide		4.5	456.0

22.	N-(3-(4-chlorophenyl)-2-phenyl-1-methylpropyl)-2-methyl-2-phenoxy-propanamide		4.3	422.2

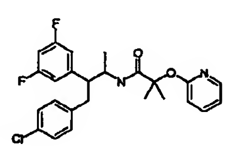
The following compounds in Table 6 were prepared following the procedures of Examples 2-3 substituting an appropriate amine for N-(2,3-diphenyl-1-methylpropylamine and appropriate carboxylic acid for 2-(4-chlorophenoxy)-2-methyl-propionic acid.

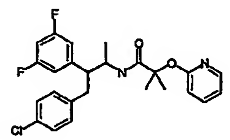
Table 6. Compounds prepared according to the methods described in Examples 2-3.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*	Diaster-eomer α and/or β
23.	*N*-[3-(4-Chlorophenyl)-2-(3,5-difluorophenyl)-1-methylpropyl]-2-methyl-2-(2-pyridyloxy)propanamide		3.9	459	α

The following compounds in Table 7 were isolated according to the procedures for separating enantiomers described in Examples 8-9.

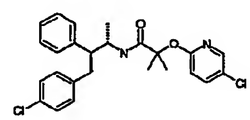
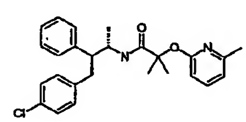
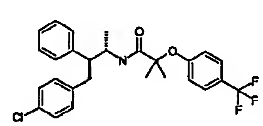
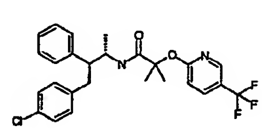
Table 7. Enantiomeric compounds isolated according to the methods described in Examples 8-9.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*	Enan-tiomer A or B
24.	*N*-[3-(4-Chlorophenyl)-2-(3,5-difluorophenyl)-1-methylpropyl]-2-methyl-2-(2-pyridyloxy)propanamide		3.9	459	A

25.	*N*-[3-(4-Chlorophenyl)-2-(3,5-difluorophenyl)-1-methylpropyl]-2-methyl-2-(2-pyridyloxy)propanamide		3.9	459	B

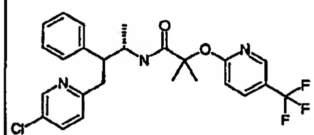
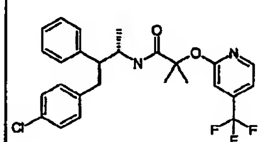
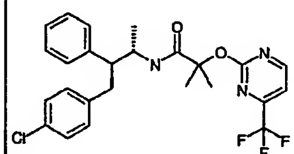
The following compounds in Table 8 were prepared with *N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-amine, hydrochloride from Reference Example 4 and the appropriate acid to afford a single enantiomer.

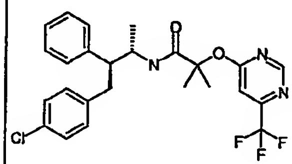
Table 8. Single enantiomeric compounds prepared with *N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-amine, hydrochloride.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*
26.	*N*-[(2*S*,3*S*)-3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(5-chloropyridyloxy)-2-methylpropanamide		4.2	457
27.	*N*-[(2*S*,3*S*)-3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(6-methylpyridyloxy)-2-methylpropanamide		3.8	437
28.	*N*-[(2*S*,3*S*)-3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(4-trifluoromethylphenyloxy)-2-methylpropanamide		4.5	490
29.	*N*-[(2*S*,3*S*)-3-(4-Chlorophenyl)-1-methyl-2-phenylpropyl]-2-(5-trifluoromethylpyridyloxy)-2-methylpropanamide		4.3	491

Examples 30-33 (Table 9) were prepared from *N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]amine, hydrochloride (Reference Example 4) or *N*-[3-(5-chloro-2-pyridyl)-2(S)-phenyl-1(S)-methylpropyl]amine, hydrochloride (Reference Example 18) and the appropriate carboxylic acid following the procedures described in Examples 2-3 (via an acyl chloride intermediate) or Example 19 (with a coupling reagent).

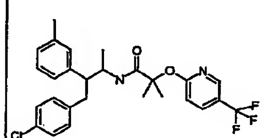
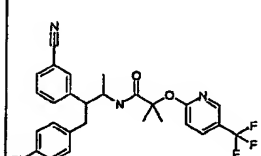
Table 9.

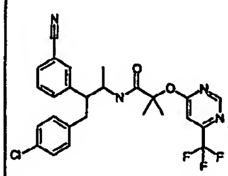
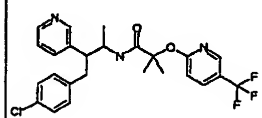
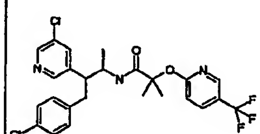
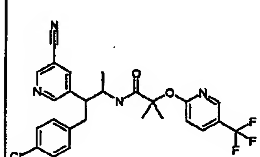
Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*
30.	*N*-[3-(5-chloro-2-pyridyl)-2(S)-phenyl-1(S)-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.7	492
31.	*N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-2-(4-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		4.3	491
32.	*N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-2-(4-trifluoromethyl-2-pyrimidyloxy)-2-methylpropanamide		3.9	492

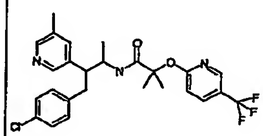
33.	*N*-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-2-(4-trifluoromethyl-4-pyrimidyloxy)-2-methylpropanamide		4.1	492

Examples 34-39 (Table 10) were prepared from the appropriate amine and acid of Reference Examples following the procedures described in Examples 2-3 (via an acyl chloride intermediate) or Example 19 (with a coupling reagent).

Table 10.

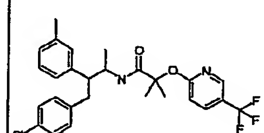
Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*	Diastereomer α and/ or β
34.	*N*-[3-(4-Chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		4.4	505	α
35.	*N*-[3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		4.1	516	α

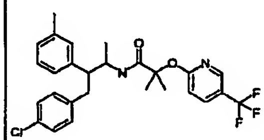
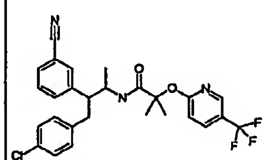
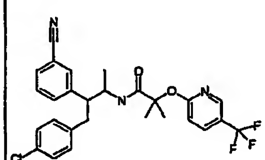
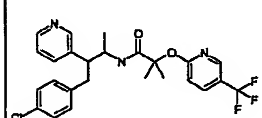
36.	*N*-[3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(6-trifluoromethyl-4-pyrimidyloxy)-2-methylpropanamide		4.0	517	α
37.	*N*-[3-(4-Chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		2.7	492	α
38.	*N*-[3-(4-Chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.9	526	α
39.	*N*-[3-(4-Chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.7	517	α

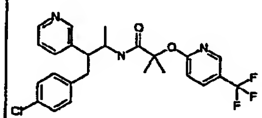
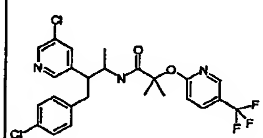
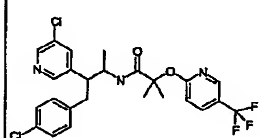
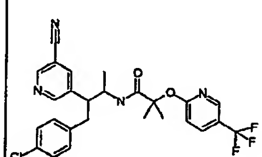
40.	*N*-[3-(4-Chlorophenyl)-2-(5-methyl-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		2.8	506	α

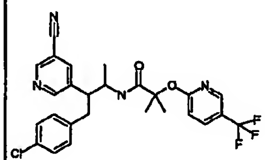
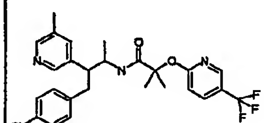
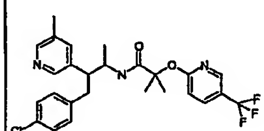
Examples 41-52 (Table 11) were isolated as single enantiomers from the corresponding racemic material (Table 10) following the procedures described in Examples 8-9 with appropriate modifications of (1) the eluent composition (4-15% ethanol/hexane), (2) flow rate (6-9 mL/min) and (3) injection volume (200 to 2000 μL).

Table 11. Enantiomeric compounds isolated according to the methods described in Examples 8-9.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum *m/e*	Enan-tiomer A or B
41.	*N*-[3-(4-chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		4.4	505	A

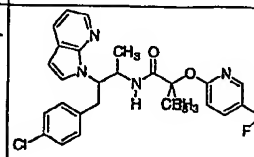
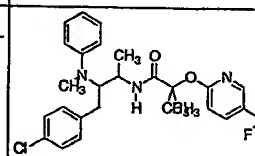
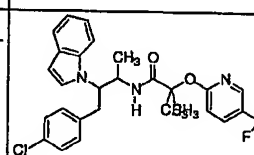
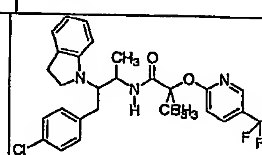
42.	*N*-[3-(4-chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		4.4	505	B
43.	*N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.9	516	A
44.	*N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.9	516	B
45.	*N*-[3-(4-Chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		2.7	492	A

46.	*N*-[3-(4-Chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		2.7	492	B
47.	*N*-[3-(4-Chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.8	526	A
48.	*N*-[3-(4-Chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.8	526	B
49.	*N*-[3-(4-Chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.7	517	A

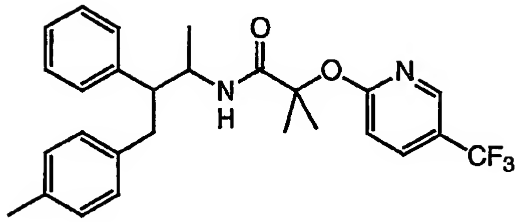
50.	*N*-[3-(4-Chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		3.7	517	B
51.	*N*-[3-(4-Chlorophenyl)-2-(5-methyl-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		2.8	506	A
52.	*N*-[3-(4-Chlorophenyl)-2-(5-methyl-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide		2.8	506	B

Examples 53-56 (Table 12) were isolated as diastereomers as indicated (Isomer A or B) on silica gel chromatography columns. The single enantiomers noted were separated on the chiral AD column noted above.

Table 12.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum m/e	Diastereomer A or B
53.	N-(3-(4-chlorophenyl)-2-(7-azaindol-N-yl)-1-methyl)propyl-2-(5-trifluoromethyl-2-oxypyridine-2 –yl)-2-methylpropanamide		3.89	532.1	B
54.	N-(3-(4-chlorophenyl)-2-(N-methyl-N-phenyl)amino-1-methyl)propyl-2-(5-trifluoromethyl-2-oxypyridine-2 –yl)-2-methylpropanamide		4.40	521	Single enantiomer derived from Isomer B
55.	N-(3-(4-chlorophenyl)-2-(indol-N-yl)-1-methyl)propyl-2-(5-trifluoromethyl-2-oxypyridine-2 –yl)-2-methylpropanamide		4.32[b,c]	531	Single enantiomer derived from Isomer B
56.	N-(3-(4-chlorophenyl)-2-(indolin-N-yl)-1-methyl)propyl-2-(5-trifluoromethyl-2-oxypyridine-2 –yl)-2-methylpropanamide		4.40'	533	B

EXAMPLE 57



2-Methyl-*N*-[1-methyl-3-(4-methylphenyl)-2-phenylpropyl]-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide

To a solution of 2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanoic acid (Reference example 14, 250 mg, 1.04 mmol) and 4-(4-methylphenyl)-3-phenylbutan-2-amine (Reference example 102, 260 mg, 1.04 mmol, mixture of 4 isomers) in CH_2Cl_2 (5.5 mL) at RT was added diisopropylethylamine (272 µl, 1.56 mmol) followed by PyBOP (649 mg, 1.25 mmol) and the reaction mixture stirred overnight. The reaction was purified by loading the reaction mixture directly onto a silica gel column and eluting from 0-30% EtOAc/hexane to give the title compound as a mixture of 4 isomers. The diastereomers were separated by HPLC on a ZORBAX RxSi column eluting 97% hexane: 3% ethanol at 20 mL/min with retention times of :

-less polar diastereomer eluted at 4.73 minutes; more polar diasteromer eluted at 5.87 minutes. The more polar diastereomer was additionally separated into enantiomers on a ChiralPak AD column eluting with 95% hexane : 5% ethanol at 8 mL/min with retention times of:

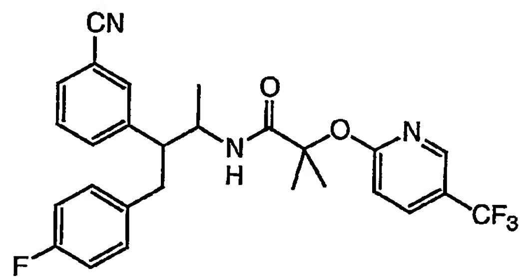
less polar enantiomer eluted at 6.84 minutes;more polar diastereomer eluted at 8.36 minutes.

Less polar diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.86 (dd, J = 8.6, 2.5 Hz, 1H), 7.19 (t, J = 3.2 Hz, 3H), 7.00 (dd, J = 21.3, 8.0 Hz, 4H), 6.91 (m, 2H), 6.83 (d, J = 8.7 Hz, 1H), 5.70 (d, J = 9.4 Hz, 1H), 4.43 (m, 1H), 3.02 (dd, J = 13.3, 6.7 Hz, 1H), 2.84 (dt, J = 7.3, 4.3 Hz, 1H), 2.84 (dd, J = 13.2, 7.7 Hz, 1H), 2.29 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H). LC-MS: m/e 471 $(M + H)^+$ (4.22 min)

More polar diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.83 (dd, J = 8.7, 2.6 Hz, 1H), 7.21 (m, 3H), 7.00 (dd, J = 30.4, 6.2 Hz, 4H), 6.82 (t, J = 9.2 Hz,

3H), 5.84 (d, J = 9.2 Hz, 1H), 4.36 (ddt, J = 9.1, 6.7, 6.6 Hz, 1H), 3.06 (dd, J = 12.8, 4.1 Hz, 1H), 2.88 (m, 1H), 2.26 (s, 3H), 1.78 (s, 3H), 1.73 (s, 3H), 0.92 (d, J = 6.6 Hz, 3H). LC-MS: m/e 471 $(M + H)^+$ (4.17 min).

EXAMPLE 58



N-[2-(3-Cyanophenyl)-3-(4-fluorophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide

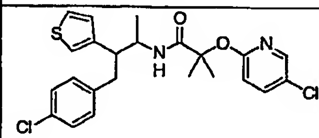
Prepared as in Example 57 only using 3-[2-amino-1-(4-fluorobenzyl)propyl]benzonitrile (Reference example 33) as the amine component to give the title compound as a mixture of 4 isomers. The diastereomers were separated by HPLC on a Zorbax RxSi column eluting 96% hexane: 4% ethanol at 20 mL/min with retention times of: less polar diastereomer eluted at 11.75 minutes; -more polar diasteromer eluted at 15.17 minutes. The more polar diastereomer was additionally separated into enantiomers on a ChiralPak AD column eluting with 92% hexane : 8% ethanol at 8 mL/min with retention times of: less polar enantiomer eluted at 9.65 minutes; more polar diastereomer eluted at 11.78 minutes.

Less polar diastereomer: ^1H NMR (500 MHz, CD_3OD): δ 8.29 (s, 1H), 7.93 (dd, J = 8.7, 2.5 Hz, 1H), 7.50 (m, 1H), 7.42 (m, 1H), 7.27 (m, 2H), 6.96-6.78 (m, 5H 5.70 (d, J = 9.6 Hz, 1H), 4.33 (m, 1H), 3.18-3.04 (m, 2H), 2.7 (dd, J = 13.5, 6.6 Hz, 1H), 1.52 (s, 3H), 1.35 (s, 3H), 1.17 (d, J = 6.6 Hz, 3H). LC-MS: m/e 500 $(M + H)^+$ (4.33 min)

More polar diastereomer: ^1H NMR (500 MHz, CD_3OD): δ 8.28 (s, 1H), 7.95 (dd, J = 8.7, 2.5 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.36 (m, 3H), 7.05 (d, J = 8.9 Hz, 3H), 6.78 (m, 2H), 6.72 (m, 2H) 4.26 (dq, J = 10, 6.6 Hz, 1H), 3.04 (dd, J = 13.7, 3.4 Hz, 1H), 2.85 (ddt J = 11.2, 3.7 Hz, 1H), 2.63 (dd, J = 13.7, 11.4 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 0.81 (d, J = 6.8 Hz, 3H). LC-MS: m/e 500 $(M + H)^+$ (4.25 min).

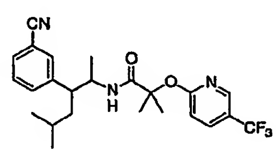
The compound of Table 13 was prepared from the appropriate amine and acid of the Reference Examples following the procedures described in Examples 2-3 (via an acyl chloride intermediate) or Examples 19 (with a coupling reagent.)

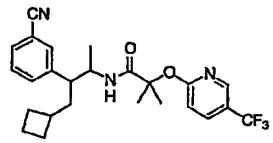
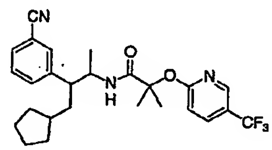
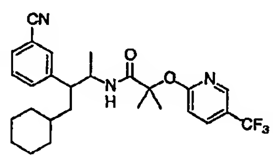
Table 13.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum m/e
59.	N-(3-(4-chlorophenyl)-1-methyl-2-(thiophen-3-yl)propyl)-2-methyl-2-(5-chloropyridin-2-yl)oxy)-2-methylpropanamide		4.21	463

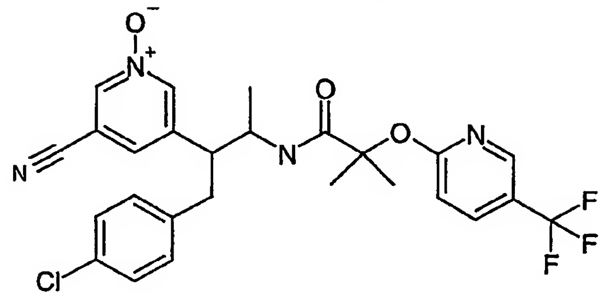
The compounds in Table 14 were isolated according to the procedure for separating enantiomers described in Examples 8-9.

Table 14. Enantiomeric compounds isolated according to the methods described in Examples 8-9.

Ex. No.	Name	Structure	retention time (min)	HPLC-mass spectrum m/e	Enantiomer A or B
60.	N-(2-(3-cyanophenyl)-1,4-dimethylpentyl)-2-methyl-2((5-(trifluoromethyl)pyridin-2-yl)oxy)-propanamide		4.0	448	B

61.	N-(2-(3-cyanophenyl)-3-cyclobutyl-1-methylpropyl)-2-methyl-2((5-(trifluoromethyl)pyridin-2-yl)oxy)-propanamide		4.1	460	B
62.	N-(2-(3-cyanophenyl)-3-cyclopentyl-1-methylpropyl)-2-methyl-2((5-(trifluoromethyl)pyridin-2-yl)oxy)-propanamide		4.18	474	B
63.	N-(2-(3-cyanophenyl)-3-cyclohexyl-1-methylpropyl)-2-methyl-2((5-(trifluoromethyl)pyridin-2-yl)oxy)-propanamide		4.29	488	B

EXAMPLE 64



Pyridine *N*-Oxide of *N*-[3-(4-Chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide (Enantiomer B)

A mixture of *N*-[3-(4-chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide (Enantiomer B, Example 50, 0.10 g, 0.19 mmol) and *m*-chloroperbenzoic acid (77%, 0.15 g, 0.67 mmol) in 2 mL of methylene chloride was stirred at room temperature for 14 h. The reaction mixture was concentrated and the residue was purified by HPLC eluting on a reverse phase C18 column with 30 to 100% acetonitrile in water (contains 0.1% trifluoroacetic acid) to give the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.58 (s, 1H), 8.32 (br s, 1H), 8.17 (s, 1H), 7.99 (br d, 1H), 7.97 (dd, 1H), 7.81 (s, 1H), 7.16 (d, 2H), 7.06 (d, 1H), 6.87 (d, 2H), 4.28 (m, 1H), 3.11 (dd, 1H), 3.01 (m, 1H), 2.71 (dd, 1H), 1.75 (s, 3H), 1.74 (s, 3H), 0.94 (d, 3H). LC-MS: m/e 533 $(M + H)^+$ (4.1 min).

EXAMPLE 65

Cannabinoid Receptor-1 (CB1) Binding Assay.

Binding affinity determination is based on recombinant human CB1 receptor expressed in Chinese Hamster Ovary (CHO) cells (Felder et al, Mol. Pharmacol. 48: 443-450, 1995). Total assay volume is 250 µl (240 µl CB1 receptor membrane solution plus 5 µl test compound solution plus 5 µl [3H]CP-55940 solution). Final concentration of [3H]CP-55940 is 0.6 nM. Binding buffer contains 50mM Tris-HCl, pH7.4, 2.5 mM EDTA, 5mM $MgCl_2$, 0.5mg/mL fatty acid free bovine serum albumin and protease inhibitors (Cat#P8340, from Sigma). To initiate the binding reaction, 5 µl of radioligand solution is added, the mixture is incubated with gentle shaking on a shaker for 1.5 h at 30°C. The binding is terminated by using 96-well harvester and filtering through GF/C filter presoaked in 0.05% polyethylenimine. The bound radiolabel is quantitated using scintillation counter.

Apparent binding affinities for various compounds are calculated from IC50 values (DeBlasi et al., Trends Pharmacol Sci 10: 227-229, 1989).

The binding assay for CB2 receptor is done similarly with recombinant human CB2 receptor expressed in CHO cells.

EXAMPLE 66

Cannabinoid Receptor-1 (CB1) Functional Activity Assay.

The functional activation of CB1 receptor is based on recombinant human CB1 receptor expressed in CHO cells (Felder et al, Mol. Pharmacol. 48: 443-450, 1995). To determine the agonist activity or inverse agonist activity of any test compound, 50 ul of CB1-CHO cell suspension are mixed with test compound and 70 ul assay buffer containing 0.34 mM 3-isobutyl-1-methylxanthine and 5.1 uM of forskolin in 96-well plates. The assay buffer is comprised of Earle's Balanced Salt Solution supplemented with 5 mM $MgCl_2$, 1 mM glutamine, 10 mM HEPES, and 1 mg/mL bovine serum albumin. The mixture is incubated at room temperature for 30 minutes, and terminated by adding 30uL/well of 0.5M HCl. The total intracellular cAMP level is quantitated using the New England Nuclear Flashplate and cAMP radioimmunoassay kit.

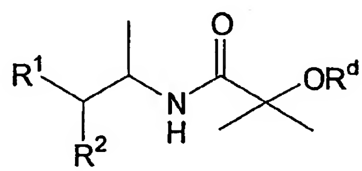
To determine the antagonist activity of test compound, the reaction mixture also contains 0.5 nM of the agonist CP55940, and the reversal of the CP55940 effect is quantitated. Alternatively, a series of dose response curves for CP55940 is performed with increasing concentration of the test compound in each of the dose response curves.

The functional assay for the CB2 receptor is done similarly with recombinant human CB2 receptor expressed in CHO cells.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from:

(1) cycloheteroalkyl,
(2) aryl,
(3) heteroaryl, and
(4) $-NR^aR^c$;

wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from R^b;

R^2 is selected from:

(1) C_{1-10}alkyl,
(2) C_{3-10}cycloalkyl-C_{1-4}alkyl,
(3) aryl-C_{1-4}alkyl,
(4) heteroaryl-C_{1-4}alkyl,

wherein each cycloalkyl, aryl and heteroaryl is optionally substituted with one to three substituents independently selected from R^b;

each R^a is independently selected from:

(1) hydrogen,
(2) methyl, and
(3) $-CF_3$;

each R^b is independently selected from:

(1) halogen,
(2) cyano,
(3) trifluoromethyl,
(4) trifluoromethoxy,
(5) C_{1-3}alkyloxy, and
(6) C_{1-3}alkyl;

R^c is independently selected from:

(1) hydrogen,
(2) C_{1-6}alkyl,
(3) aryl,
(4) heteroaryl,
(5) aryl-methyl, and
(6) heteroaryl-methyl,

each R^c may be unsubstituted or substituted with one to three substituents selected from R^h;

R^d is independently selected from:

(1) cycloalkyl,
(2) aryl,
(3) heteroaryl,

each R^d may be unsubstituted or substituted with one to three substituents selected from R^h;

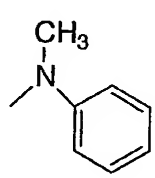
each R^h is independently selected from:

(1) halogen,
(2) C_{1-3}alkyl,
(3) -CN, and
(4) $-CF_3$;

wherein when pyridyl groups are unsubstituted on nitrogen, they may optionally be present as the N-oxide.

2. The compound according to Claim 1, wherein R^1 is selected from:

(1) phenyl,
(2) pyridyl,
(3) indolyl,
(4) 7-aza-indolyl,
(5) thiophenyl, and
(6)



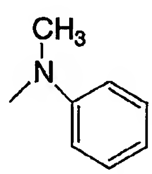
;

wherein each aryl and heteroaryl is optionally substituted with one or two substitutents independently selected from R^b, and each pyridyl may be optionally present as the N-oxide;

and pharmaceutically acceptable salts thereof.

3. The compound according to Claim 2, wherein R^1 is selected from:

(1) phenyl,
(2) 3-cyanophenyl,
(3) 3-methylphenyl,
(4) 3,5-difluorophenyl,
(5) 3-pyridyl,
(6) 5-chloro-3-pyridyl,
(7) 5-methyl-3-pyridyl,
(8) 5-cyano-3-pyridyl,
(9) 1-oxido-5-cyano-3-pyridyl,
(10) 1-indolyl,
(11) 7-aza-indol-N-yl,
(12) 2-thiophenyl, and
(13)



;

and pharmaceutically acceptable salts thereof.

4. The compound according to Claim 3, wherein R^1 is 5-cyano-3-pyridyl; and pharmaceutically acceptable salts thereof.

5. The compound according to Claim 2, wherein R^2 is selected from:

(1) C_{1-6}alkyl,
(2) C_{3-6}cycloalkylmethyl,
(3) phenylmethyl,
(4) heteroarylmethyl,

wherein each cycloalkyl, aryl and heteroaryl is optionally substituted with one to three substituents independently selected from R^b, and pharmaceutically acceptable salts thereof.

6. The compound according to Claim 5, wherein R^2 is selected from:
(1) 2-methylpropyl,
(2) n-pentyl,
(3) cyclobutylmethyl,
(4) cyclopentylmethyl,
(5) cyclohexylmethyl,
(6) benzyl,
(7) 4-chlorobenzyl,
(8) 4-methylbenzyl,
(9) 4-fluorobenzyl,
(10) 4-methoxybenzyl, and
(11) (5-chloro-2-pyridyl)methyl;
and pharmaceutically acceptable salts thereof.

7. The compound according to Claim 2, wherein R^d is selected from:
(1) C_{4-6}cycloalkyl,
(2) aryl,
(3) heteroaryl,
wherein R^d may be unsubstituted or substituted with one or two substituents selected from R^h,
and pharmaceutically acceptable salts thereof.

8. The compound according to Claim 7, wherein R^d is selected from:
(1) phenyl,
(2) pyridyl, and
(3) pyrimidinyl,
wherein R^d may be unsubstituted or substituted with one or two substituents selected from R^h;
and pharmaceutically acceptable salts thereof.

9. The compound according to Claim 8, wherein R^d is selected from:

(1) phenyl,
(2) 4-chlorophenyl,
(3) 3-chlorophenyl,
(4) 3,5-difluorophenyl,
(5) 3,5-dichlorophenyl,
(6) 2-pyridyl,
(7) 5-chloro-2-pyridyl,
(8) 6-methyl-2-pyridyl,
(9) 5-trifluoromethyl-2-pyridyl,
(10) 4-trifluoromethyl-2-pyridyl,
(11) 4-trifluoromethyl-2-pyrimidyl, and
(12) 6-trifluoromethyl-4-pyrimidyl;

and pharmaceutically acceptable salts thereof.

10. The compound according to Claim 1, selected from:

(1) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(4-chlorophenyloxy)-2-methylpropanamide;
(2) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(2-pyridyloxy)-2-methylpropanamide;
(3) *N*-[3-(4-chlorophenyl)-1-methyl-2-(3-pyridyl)propyl]-2-(4-chlorophenyloxy)-2-methylpropanamide;
(4) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3,5-difluorophenyloxy)-2-methylpropanamide;
(5) *N*-[3-(4-chlorophenyl)-2-phenyl-1-methylpropyl]-2-(3,5-dichlorophenyloxy)-2-methylpropanamide;
(6) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(3-chlorophenyloxy)-2-methylpropanamide;
(7) *N*-[3-(4-chlorophenyl)-2-(3,5-difluorophenyl)-1-methylpropyl]-2-(2-pyridyloxy)-2-methylpropanamide;
(8) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenyl-propyl]-2-(5-chloro-2-pyridyloxy)-2-methylpropanamide;

(9) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(6-methyl-pyridyloxy)-2-methylpropanamide;

(10) *N*-[3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(phenyloxy)-2-methylpropanamide;

(11) *N*-[(3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(5-trifluoromethylpyridyloxy)-2-methylpropanamide;

(12) *N*-[3-(4-chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(13) *N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(14) *N*-[3-(4-chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(15) *N*-[3-(4-chlorophenyl)-2-(5-methyl-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(16) *N*-[3-(4-chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(17) *N*-[3-(4-chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(18) *N*-[3-(4-chlorophenyl)-2-phenyl-1-methylpropyl]-2-(4-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(19) *N*-[3-(4-chlorophenyl)-2-phenyl-1-methylpropyl]-2-(4-trifluoromethyl-2-pyrimidyloxy)-2-methylpropanamide;

(20) N-[3-(4-chlorophenyl)-1-methyl-2-(thiophen-3-yl)propyl]-2-(5-chloro-2-pyridyloxy)-2-methylpropanamide;

(21) *N*-[3-(5-chloro-2-pyridyl)-2-phenyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(22) *N*-[3-(4-methyl-phenyl)-1-methyl-2-phenylpropyl]-2-(4-trifluoromethyl-phenyloxy)-2-methylpropanamide;

(23) *N*-[3-(4-fluoro-phenyl)-2-(3-cyano-phenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(24) N-[3-(4-chlorophenyl)-2-(1-indolyl)-1-methyl)propyl]-2-(5-trifluoromethyl-2-oxypyridine-2–yl)-2-methylpropanamide;

(25) N-[3-(4-chlorophenyl)-2-(7-azaindol-N-yl)-1-methyl)propyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(26) *N*-[3-(4-chloro-phenyl)-2-(1-indolinyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(27) *N*-[3-(4-chloro-phenyl)-2-(N-methyl-anilino)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(28) *N*-[3-(4-methoxy-phenyl)-2-(3-cyano-phenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(29) *N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(6-trifluoromethyl-4-pyrimidyloxy)-2-methylpropanamide;
(30) N-[2-(3-cyanophenyl)-1,4-dimethylpentyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(31) N-[3-(4-chlorophenyl)-2-(1-oxido-5-cyano-3-pyridyl]-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(32) N-[2-(3-cyanophenyl)-3-cyclobutyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(33) N-[2-(3-cyanophenyl)-1-methyl-heptyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(34) N-[2-(3-cyanophenyl)-3-cyclopentyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(35) N-[2-(3-cyanophenyl)-3-cyclohexyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

11. The compound according to Claim 9, wherein R^d is 5-trifluoromethyl-2-pyridyl;
and pharmaceutically acceptable salts thereof.

12. The compound according to Claim 11 selected from:
(1) *N*-[(3-(4-chlorophenyl)-1-methyl-2-phenylpropyl]-2-(5-trifluoromethylpyridyloxy)-2-methylpropanamide;
(2) *N*-[3-(4-chlorophenyl)-2-(3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(3) *N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;
(4) *N*-[3-(4-chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(5) *N*-[3-(4-chlorophenyl)-2-(5-methyl-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(6) *N*-[3-(4-chlorophenyl)-2-(5-cyano-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(7) *N*-[3-(4-chlorophenyl)-2-(3-methylphenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(8) *N*-[3-(5-chloro-2-pyridyl)-2-phenyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(9) *N*-[3-(4-fluoro-phenyl)-2-(3-cyano-phenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(10) N-[3-(4-chlorophenyl)-2-(1-indolyl)-1-methyl)propyl]-2-(5-trifluoromethyl-2-oxypyridine-2–yl)-2-methylpropanamide;

(11) N-[3-(4-chlorophenyl)-2-(7-azaindol-N-yl)-1-methyl)propyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(12) *N*-[3-(4-chloro-phenyl)-2-(1-indolinyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(13) *N*-[3-(4-chloro-phenyl)-2-(N-methyl-anilino)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(14) *N*-[3-(4-methoxy-phenyl)-2-(3-cyano-phenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(15) N-[2-(3-cyanophenyl)-1,4-dimethylpentyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(16) N-[3-(4-chlorophenyl)-2-(1-oxido-5-cyano-3-pyridyl]-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(17) N-[2-(3-cyanophenyl)-3-cyclobutyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(18) N-[2-(3-cyanophenyl)-1-methyl-heptyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(19) N-[2-(3-cyanophenyl)-3-cyclopentyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

(20) N-[2-(3-cyanophenyl)-3-cyclohexyl-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

13. A composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

14. The use of a compound according to Claim 1, for the manufacture of a medicament useful for the treatment of a disease mediated by the Cannabinoid-1 receptor in a human patient in need of such treatment.

15. The use according to Claim 14 wherein the disease mediated by the Cannabinoid-1 receptor is an eating disorder associated with excessive food intake.

16. The use according to Claim 15 wherein the eating disorder associated with excessive food intake is obesity.

17. The use of a compound according to Claim 1 for the manufacture of a medicament for the prevention of obesity in a person at risk therefor.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/US 03/07039

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C235/20 C07C235/10 C07B61/00 C07D213/61 C07D213/40
C07D235/10 A61K31/165 A61K31/435 A61K31/505 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07B C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 41519 A (CHRISTENSEN SIEGFRIED B ;SMITHKLINE BEECHAM CORP (US); BENDER PAUL) 24 September 1998 (1998-09-24) cited in the application the whole document	1-17
A	WO 02 068388 A (WYVRATT MATTHEW J ;CHU LIN (US); GOULET MARK T (US); WARNER DANIEL) 6 September 2002 (2002-09-06) the whole document	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	26/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/US 03/07039

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